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Selective Fluorination Strategies

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Abstract

There is a great interest in the synthesis of fluorinated aromatic and heterocyclic compounds, which have a range of applications in the pharmaceutical industry. Many common routes to these compounds, however, are low yielding and/or expensive. This thesis is concerned with novel methods for the synthesis of fluoro-aromatics and fluoro-pyrazoles using conventional fluorinating agents, such as Selectfluor™, as well as using elemental fluorine and the flow reactor technology developed in Durham.

Firstly, elemental fluorine was used to fluorinate a range of aromatics containing electron-donating substituents, using both batch and flow methods. These methods often afforded the desired compound but with little selectivity and low conversion from the starting materials. Following on from this, *ipso* fluoro-deboronation techniques using Selectfluor™, were employed to improve the selectivity and yields of the reaction and, in many cases, the desired mono-fluorinated arylfluoride could be accessed in good yield. A range of aryl boronic acid derivatives were explored as the substrate and the results showed that trifluoroborate salts were the most useful substrate. The *ipso* fluoro-deboronation of heterocyclic boronic acid derivatives was also investigated and showed some promising results.

The synthesis of 4-fluoropyrazoles was investigated using three methods. Initially, a two-step process, where the 2-fluoro-1,3-diketone was synthesised and isolated and subsequently reacted with hydrazine, was employed. This allowed a range of 4-fluoropyrazoles to be obtained in high yield and purity. Secondly, a telescoped two-step continuous flow process was employed which did not require isolation of the intermediate 2-fluoro-1,3-diketone. This reaction gave good yields and required less solvent with significantly lower reaction times than the two-step process. Thirdly, C-4 mono- and di-fluorination of 3,5-disubstituted pyrazoles was investigated using Selectfluor™ and elemental fluorine. This method gave low conversion from the starting material (50–60 %) but the desired 4-fluoropyrazoles and novel 4,4-difluoropyrazoles could be isolated.

Acknowledgements

Firstly I would like to thank everyone who has made the last three years so memorable. I would particularly like to thank my academic supervisor, Professor Graham Sandford for his invaluable help and support throughout the course of my Ph.D. I would also like to thank my industrial supervisors, Dr Jonathan Fray and Miss Bhairavi Patel, for their input and enthusiasm and Pfizer for funding.

This research would not have been possible without the help of the highly professional technical staff at Durham University, namely: Dr Alan Kenwright, Mr Ian McKeag, Mrs Catherine Heffernan (NMR); Dr Jackie Mosely, Mr Peter Stokes, Mr David Parker (Mass spectrometry); Miss. Judith Magee (Elemental analysis); Dr Dmitrii Yufit (X-ray crystallography); Mr Lenny Lauchlan and Dr Aileen Congreve (Chromatography); Mr Malcom Richardson (Glassblowing) and Mr Dave Hunter (High Pressure Facilities). I would like to give a special mention to the late Mr Peter Coyne (Glassblowing) for showing me a smile every time I saw him.

I would like to thank all members of the fluorine group, past and present, particularly Prof. Richard Chambers, Graham Pattison, Ian Wilson, Christopher McPake, Matthew Cargill, Lawrence Hill, Ffion Abraham, Katharine Linton and Peter Harrison (honorary member). I would also like to thank my family and Peter Harvey for their love and support.

Memorandum

The work described in this thesis was carried out at Durham University between October 2008 and December 2011. This thesis is the work of the author, except where acknowledged by reference, and has not been submitted for any other degree. The copyright of this thesis rests with the author. No quotation from it should be published without the prior written consent and information derived from it should be acknowledged.

Part of this work has been the subject of the following:

- J. R. Breen, G. Sandford, D. S. Yufit, J. A. K. Howard, J. Fray, and B. Patel, *Beilstein J. Org. Chem.*, 2011, **7**, 1048-1054

This work has been presented, in part, at:

- 16th European Symposium on Fluorine Chemistry, Ljubljana, Slovenia, July 2010
- 10th RSC Fluorine Subject Meeting, Durham, UK, September 2010
- Departmental Postgraduate Symposium, Durham University, UK, June 2011
- ACS National Meetings & Exposition, Denver, Colorado, USA, August 2011
- 11th RSC Fluorine Subject Meeting, Aberdeen, UK, September 2011
- NORSC Green Chemistry Postgraduate Meeting, York, UK, October 2011

Nomenclature and Abbreviations

Chemical

Ac	Acetyl
Ar	Aryl
BOC	<i>t</i> -butyloxycarbonyl
Bu	Butyl
Cat	Catalyst
Conc	Concentration
DABCO	1,4-Diazabicyclo[2.2.2]octane
DAST	(Diethylamino)sulfur trichloride
DCM	Dichloromethane
DIPEA	<i>Diisopropylethylamine</i>
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
E	Electrophile
EDG	Electron-donating group
EI	Electron ionisation
EWG	Electron-withdrawing group
ES	Electrospray
Et	Ethyl
GC-MS	Gas chromatography-mass spectrometry
h	Hours
IR	Infra-red
J	Coupling constant, Hz
LC-MS	Liquid chromatography-mass spectrometry
Me	Methyl
MeCN	Acetonitrile (methyl cyanide)
Min	Minutes
Mol	Moles
m.p.	Melting point
MW	Microwave

NBS	<i>N</i> -Bromosuccinimide
NCS	<i>N</i> -Chlorosuccinimide
NFSI	<i>N</i> -Fluorobenzenesulfonimide
NMR	Nuclear magnetic resonance
PET	Positron emission tomography
Ph	Phenyl
Pin	Pinacol ester
pK _a	Acid dissociation constant
ppm	Parts per million
Pr	Propyl
PTFE	Polytetrafluoroethylene
R	Alkyl
RT	Room temperature
SET	Single electron transfer
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	Tosyl
UV	Ultraviolet
X	Halogen
Δ	Heat
δ	Chemical shift/ppm

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Chapter 1

Introduction

1.1 Overview

1.1.1 Fluorine – Isolation and History

The isolation of fluorine gas occupied researchers for many years and one of the first important steps in the synthesis was the preparation of concentrated hydrofluoric acid (HF) by Thénard and Gay-Lussac.¹ The substance fumed strongly in air, rapidly dissolved glass, and caused extraordinary burns on contact with the skin because researchers were not used to handling anhydrous HF.

Fluorine was finally isolated successfully over a century ago by Moissan² who gained a Nobel Prize in 1906 for his achievement. Moissan produced fluorine by electrolyzing a solution of potassium hydrogen difluoride (KHF₂) in non-conducting liquid anhydrous hydrogen fluoride. The electrolytic cell was constructed from platinum/iridium electrodes in a platinum holder and the apparatus was cooled to -50 °C. The result was to isolate the hydrogen from the anode and fluorine at the cathode. Today, fluorine is still manufactured using this electrochemical process.

The first large-scale production of fluorine was undertaken in association with the Manhattan Project during World War II, where uranium hexafluoride (UF₆) was used to allow separation of the ²³⁵U and ²³⁸U isotopes. The radioactive uranium was used for the construction of the first atomic bombs in 1945 and uranium refining for nuclear energy is still one of the major uses for elemental fluorine.

1.1.2 Properties of the Fluorine Atom

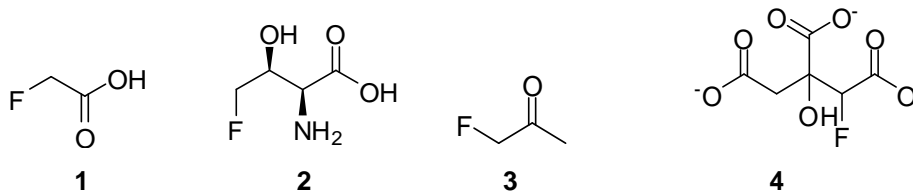
Fluorine is the most abundant halogen in the earth's crust, present in various ores. The fluorine atom has a van der Waals radius of 1.47 Å, a size more comparable to that of oxygen (1.52 Å) than to that of the other halogens (chlorine, 1.8 Å; bromine, 1.95 Å; iodine, 2.15 Å). Fluorine has an electronegativity of 4.0 compared to an electronegativity of 3.0 for chlorine and 2.8 for bromine and the high electronegativity of fluorine results in the strong polarity of the carbon-fluorine bond, making the carbon-fluorine bond the strongest covalent bond to carbon. For mono-fluorinated alkanes, the carbon-fluorine bond is 25 kcal/ mol stronger than that of the carbon-chlorine bond. The strength of the C–F bond can be demonstrated by the stability of monofluoroacetate, which can withstand boiling with 100 % sulfuric acid without any de-fluorination. This stability is also the reason for the potentially significant environmental effects of some organo-fluorine compounds.

Fluorine atoms also possess three pairs of electrons in their outer electronic shell that are not involved in bonding with any other atoms, which can have an effect on physical properties of fluorinated systems. These non-bonding electrons surrounding each fluorine atom can, in highly fluorinated systems such as polytetrafluoroethylene (PTFE), be regarded as a protective sheath that shields the carbon backbone of each molecule from chemical attack, providing many highly fluorinated systems with very high thermal and chemical stability.³

1.1.3 Carbon-fluorine Bonds in Organic Synthesis

Very few naturally occurring compounds containing a carbon-fluorine bond exist and the regio-selective introduction of fluorine atoms into organic systems can be very difficult. Over 3700 naturally occurring organo-halogens are now known to exist but only relatively few contain fluorine. The most common natural organo-fluorine species is fluoroacetate (**1**) which was the first naturally occurring organo-fluorine compound to be identified in 1943 and is a metabolite of the Southern African plant *Dichapetalum cymosum*. The most recently discovered, structurally novel, fluorine-containing natural

product was 4-fluorothreonine (**2**) isolated from the bacterium *Streptomyces cattleya* in 1986.⁴ Others include fluoroacetone (**3**) and fluorocitrate (**4**).



The number of man-made fluorinated organic molecules has dramatically increased over the past few years due to their many useful properties and, indeed, many chemical products including surfactants, dyes, anaesthetics, pharmaceuticals and plant-protection agents are fluorine containing molecules. The addition of fluorine atoms into organic compounds can have a huge effect on the biological properties of a molecule and thus can be extremely useful to, for example, the pharmaceutical industry. The properties of the wide range of organo-fluorine compounds are nearly impossible to compare as a group. William R. Dolbier Jr⁵ said that "Oftentimes, a fluorine atom isn't noticed in terms of size, yet it can have a really strong impact" and furthermore "every time you see a biologically active molecule that has fluorine in it, it could be in there for a different reason".

1.2 Fluorine in the Pharmaceutical Industry

Since organo-fluorine compounds are almost non-existent as natural products, it is a surprise that today 20–25 % of pharmaceuticals contain at least one fluorine atom, which are used in the treatment of a variety of clinical areas including those of the central nervous system, cardiovascular diseases, obesity, antibacterial agents, and antifungal therapy.

Fluorinated drugs have constituted approximately 5–15 % of the total number of drugs launched worldwide over the past 50 years with a clear increase in the last 5 years and since June 2004 there have been 44 fluorinated drugs under investigation in phase III trials⁶. The early successful introductions of fluorinated steroids and 5-fluorouracil were

followed by a steady succession of fluorinated drugs with the launch of one to three candidates per year until the early 1980s.⁷

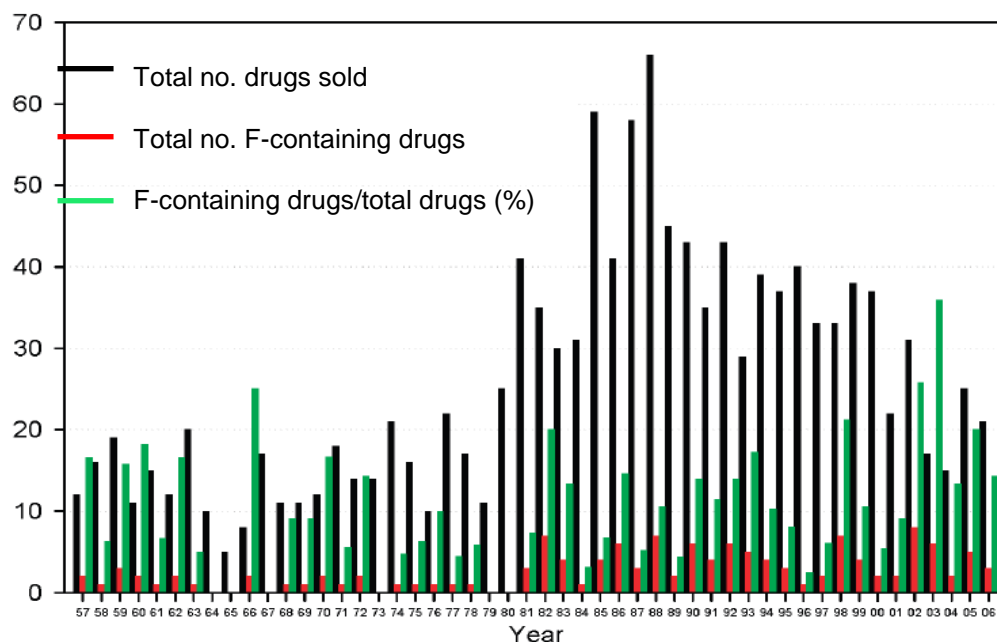
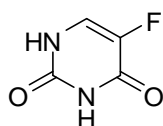
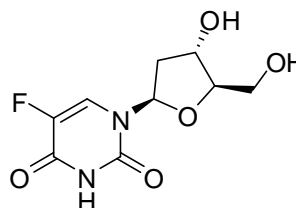


Figure 1: Number of drugs sold between 1957 and 2006

Fluorine substitution has played, and continues to play, an important role in the development of more active and more selective agents to treat diseases. One of the earliest synthetic fluorinated drugs is the anti-neoplastic agent 5-fluorouracil,⁸ an anti-metabolite first synthesised in 1957. It shows high anticancer activity by inhibiting the enzyme thymidylate synthase, thereby preventing the cellular synthesis of thymidine. Since the advent of 5-fluorouracil (**5**), fluorine substitution is commonly used in contemporary medicinal chemistry to improve metabolic stability, bioavailability and protein–ligand interactions. An increasing number of related fluorinated anti-tumour agents have now becoming available as cancer treatments, including 5-fluoro-2'-deoxyuridine (**6**) and its derivatives.⁹

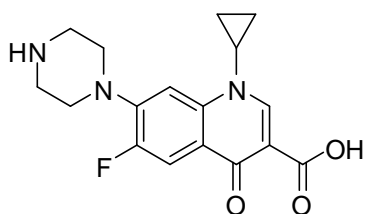


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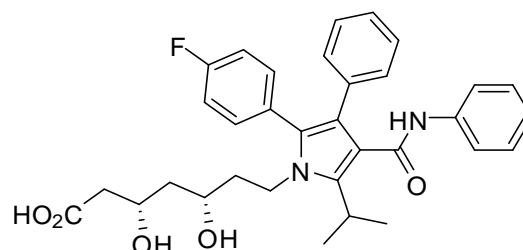


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The development of pharmacological agents able to counteract the mechanisms of drug resistance in oncology has remained a major goal for the past two decades. Fluorinated organic molecules are known to perform a wide range of biological functions and fluorinated anti-cancer agents have become a focus in the development of new therapies for cancer.¹⁰ Other drugs containing fluorine, such as Cipro (7) (Bayer AG), further show the importance of fluorine in drugs as this was one of the worldwide top 20 bestselling drugs of 1993. More recently, the fluorine containing drug, Lipitor (8) (Pfizer), which is a member of the statin drug class used for lowering blood cholesterol, was the bestselling drug of 2007.



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A variety of reasons are behind the huge importance of fluorine substituents present in drugs. Substitution of hydrogen by fluorine can change the conformational preferences of a small molecule because of size and stereo-electronic effects as well as the pK_a and lipophilicity of the molecule, as discussed below.

1.2.1 pK_a

The introduction of fluorine in to a molecule can have a significant effect on the acidity or basicity of a molecule due to its large inductive electron-withdrawing effect. The effect is predictable as pK_a generally decreases on increasing fluorination, as shown, for example, by the pK_a 's of fluorinated acetic acids (Figure 2). Similarly, alcohols, carboxylic acids, heterocycles, and phenols all become more acidic with adjacent fluorine substitution.

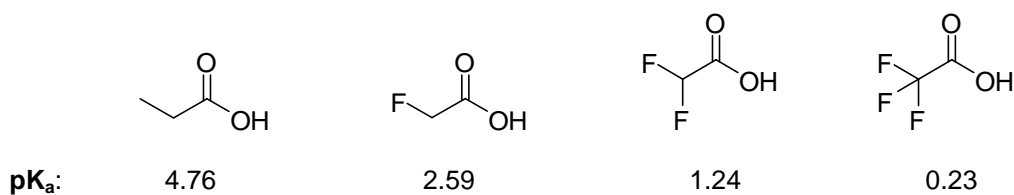


Figure 2: *pK_a values of fluorinated acetic acids*

The pK_a of a drug can also have an impact on its bioavailability. For example, in a series of 3-piperidinyndole antipsychotic drugs, it was found that fluorination decreased the basicity of the amine, thereby improving bioavailability.¹¹ Changes in pK_a can have effects on a variety of other parameters including physio-chemical properties (solubility), binding affinities (potency and selectivity), absorption, distribution, metabolism and safety issues.⁶

1.2.2 Lipophilicity

For a drug molecule to pass through a cell membrane its lipophilicity must be such that it can pass into the lipid core but not become trapped within it. Biological absorption and distribution are largely controlled by the ionisation state and the balance of lipophilicity and hydrophilicity in a drug molecule. Enhanced lipophilicity can increase the measured binding free energy through more favourable partitioning between the polar aqueous solution and the less polar receptor site. A well-known measure of lipophilicity is the logarithmic coefficient (log D) for distribution (D) of a compound between *n*-octanol and water at pH 7.4.

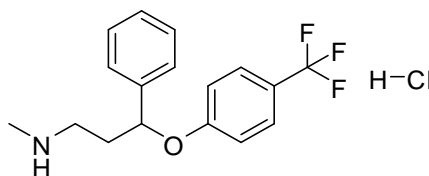
In general, exchange of a hydrogen atom by fluorine most often leads to a more lipophilic molecule, however, there are exceptions where the log D value is decreased but this is generally found in aliphatic chains due to the strong electron withdrawing nature of fluorine.¹² Aromatic fluorination or fluorination next to atoms with π -bonds increases lipophilicity due to the good overlap between the fluorine 2s or 2p orbitals with the corresponding orbitals on carbon. This makes the C–F bond non-polarisable, and, therefore, contributes to increased lipophilicity of the whole molecule.¹³

1.2.3 Protein Binding Affinity

Both electronic and steric effects are important when discussing protein binding affinity and the introduction of fluorine may influence both of these properties.

1.2.3.1 Steric Effects

Substitution of a hydrogen or hydroxyl group for a fluorine in biologically active molecules is tolerated because the fluorine van der Waals radius (1.47 Å) is in-between that of oxygen (1.57 Å) and hydrogen (1.20 Å). Fluorine substitution, therefore, only changes the steric demand at receptor sites slightly. This can be seen by the use of the fluorovinyl group (C=CHF) as a replacement for the peptide amide bond. The introduction of a trifluoromethyl group within a molecule, however, can change the steric bulk significantly as its van der Waals volume is estimated to be similar to that of an *iso*-propyl group, with both groups having an effective van der Waals radius of 2.20 Å.¹³ These steric variations combined with the high electronegativity of the fluorine atom, can lead to changes in preferred molecular conformation upon fluorine substitution which can be seen in Prozac (**9**).



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Prozac acts by selectively inhibiting the reuptake of serotonin, allowing the neurotransmitter to activate its specific receptor. Structure–activity relation studies showed that the inclusion of a trifluoromethyl group in the para position of the phenolic ring increases the potency for inhibiting 5-HT uptake 6-fold, compared to the non-fluorinated parent compound. It is believed that the steric bulk of the trifluoromethyl group at this position allows the phenoxy- ring to adopt a conformation which favours binding to the serotonin transporter.¹¹

1.2.3.2 Electrostatic Interactions

It has been shown that the C–F bond dipole adopts a Burgi–Dunitz type trajectory to amide carbonyl groups on the peptide backbone. This electrostatic effect is weak relative to other protein–ligand binding interactions but the C–F bond dipole contributes to optimising how drugs orientate at the binding site of their target enzyme/protein.¹⁴

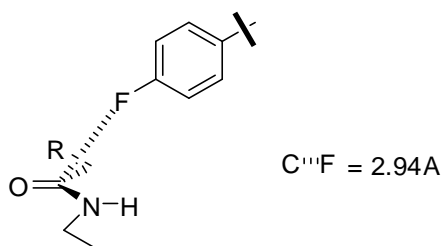
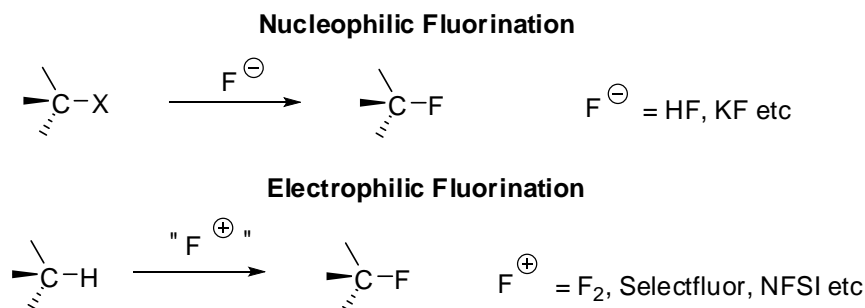


Figure 3: C–F bond dipole adopting a Burgi–Dunitz type trajectory

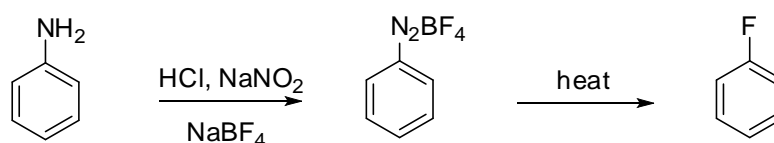
1.3 Fluorination Methods

The majority of organo-fluorine compounds, such as important pharmaceuticals discussed above, that now exist must be prepared by synthetic procedures since there are so few naturally occurring fluorinated precursors. The key step is the synthesis of a carbon–fluorine bond at some point during a synthesis and many fluorinating agents have been developed over the years with the goal of solving this problem, which has had varying degrees of success.¹⁵ Recently, research has focused on finding ways of introducing fluorine into specific sites within small molecules to provide building blocks for the preparation of biologically active compounds, which have more complex structures, but there is also huge interest in being able to introduce a fluorine atom at a late stage of a drug synthesis. In general, there are two main methods of fluorination: nucleophilic and electrophilic fluorination (Scheme 1).



Scheme 1: *Nucleophilic and electrophilic fluorination*

Nucleophilic fluorination uses substances such as KF, HF, TBAF and DAST in reactions with appropriately functionalised precursors. In the past, fluorinated aromatic compounds were synthesised by multi-step processes such as the Balz-Schiemann reaction where aromatic amines are converted into diazonium tetrafluoroborates, which thermally decompose with formation of mono-fluorinated aromatic compounds (Scheme 2).

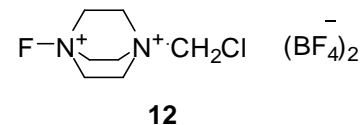
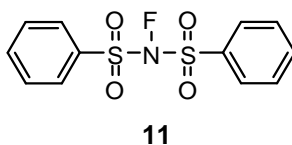
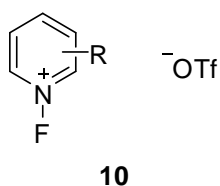


Scheme 2: *Balz-Schiemann reaction*

1.3.1 Electrophilic Fluorination Methods

The most direct method for the introduction of fluorine atoms into an organic system is the replacement of hydrogen by fluorine which requires the use of an electrophilic fluorinating agent. A variety of these reagents have been developed over the years including: perchloryl fluoride, xenon difluoride and fluoroxy compounds such as acyl hypofluorites as well as N-F reagents and elemental fluorine.

Many N-F reagents have been synthesised for electrophilic fluorination reactions such as N-fluoropyridinium salts (**10**), *N*-Fluorobenzenesulfonimide¹⁶ (NFSI) (**11**), and Selectfluor™ (**12**).



The most useful of these reagents, SelectfluorTM and elemental fluorine will be discussed in more detail with a brief overview of the processes for the selective, electrophilic fluorination of aromatic, heterocyclic and dicarbonyl systems which will be discussed further in this thesis.

1.3.1.1 SelectfluorTM

SelectfluorTM (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octanebis(tetrafluoroborate))¹⁷ is an extremely stable, virtually non-hygroscopic crystalline fluorinating agent which does not require special handling techniques. The most practical procedure for the production of **12** involves the preparation of the precursor by initial alkylation of 1,4-diazabicyclo[2.2.2]octane (dabco, also known as triethylenediamine (TEDA)) with dichloromethane as the solvent. After counter-ion exchange with sodium tetrafluoroborate and subsequent precipitation of sodium chloride from the acetonitrile solution, fluorination with F₂ provides the desired product. Variations on this process allow the production of **12** on an industrial scale and the production of various fluorinated derivatives.¹⁸

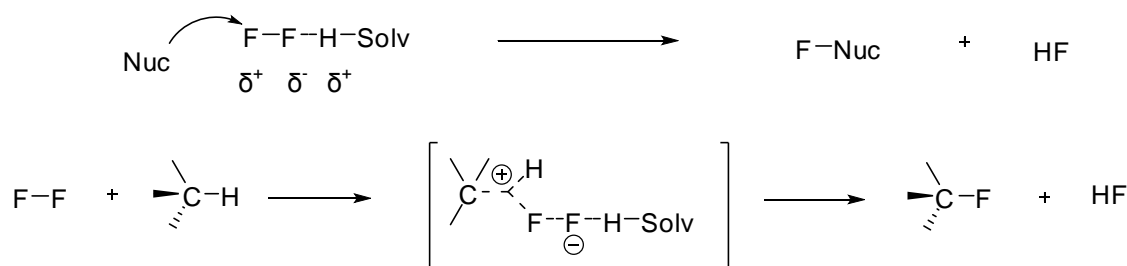
SelectfluorTM has since been used in the fluorination of many substrates including dicarbonyl compounds¹⁹, substituted aromatic systems²⁰ and nitro compounds²¹. The main drawback of **12** is that it is only soluble in water, acetonitrile (MeCN), *N,N*-dimethylformamide (DMF) and dimethylsulfoxide (DMSO) and only sparingly soluble in ethanol and acetone. Recently, the use of ionic liquids, such as triflate, tetrafluoroborate, and phosphorous hexafluoride salts of 1-ethyl-3-methylimidazolium or 1-butyl-3-ethylimidazolium¹⁸ have received attention as reusable and environmentally friendly media for industrial fluorination reactions using **12**.

1.3.1.2 Elemental Fluorine

The least expensive and most reactive electrophilic fluorinating agent is fluorine gas itself. Elemental fluorine is now beginning to be accepted by many organo-fluorine chemists as a viable reagent for synthesis of carbon-fluorine bonds in a range of organic systems.

A problem in performing selective and efficient electrophilic fluorination of organic compounds using fluorine is related to the low dissociation energy of the fluorine-fluorine bond and the strength of the fluorine-carbon bond formed. A solution to this problem is based around controlling the extreme reactivity of elemental fluorine by various methods, such as, by dilution of the fluorine by an inert gas, for example nitrogen, and using low reaction temperatures and appropriate solvents.

Selective direct fluorination (the replacement of one or two hydrogen atoms by fluorine) is usually carried out in conditions that favour nucleophilic attack by the substrate on electrophilic fluorine. Rozen *et al*²² showed that polar solvents encourage polarisation of the fluorine molecule, which makes it more susceptible to nucleophilic attack and acts as an acceptor for the counter-ion (fluoride ion) in the transition state (Scheme 3). Consequently, the reaction media of choice for selective direct fluorination reactions are either high dielectric aprotic solvents such as acetonitrile or strong protonic acids such as formic or sulfuric acids.²³ Recently, acetonitrile has been used as an effective solvent and is thought either to enhance fluorination by acting as a polar solvent or by reaction with fluorine to form a transient electrophilic N-F derivative that acts as the fluorinating agent.²⁴



Scheme 3: The interaction of solvent with elemental fluorine

Elemental fluorine can be used for a wide range of reactions including the direct fluorination of aromatics, aliphatics, diketones and heterocycles¹⁵ as discussed below.

1.3.1.2.1 Safe Use of Fluorine

Pure fluorine gas (F_2) is corrosive to exposed tissues, to the upper and lower respiratory tracts and can penetrate deeply into body tissues. It will continue to exert toxic effects unless neutralized because it reacts violently and decomposes to hydrofluoric acid (HF) on contact with moisture. Fluorine is one of the most powerful oxidizing agents known and reacts with virtually all inorganic and organic substances, for example, it ignites in contact with ammonia, ceramic materials, phosphorus, sulfur, copper wire, acetone and many other organic and inorganic compounds. Furthermore, HF, produced upon transfer of C–H to C–F as a by-product, is corrosive and readily destroys tissue. Exposure of the eyes to HF may result in blindness or permanent eye damage. HF also easily penetrates human skin, allowing it to destroy soft tissues and decalcify bone. Chemical burns from HF are typically very painful and slow to heal and skin exposure to high concentrated HF (approximately 50 % or greater) immediately results in serious and painful destruction of tissue. Not only can skin contact cause burns, but systemic fluoride poisoning may also occur. Skin contact with HF at lower concentrations may not produce pain or burning sensations until hours after the exposure and inhaling HF vapours can seriously damage the lungs. Calcium gluconate gel is a topical antidote for HF skin exposure. Calcium gluconate works by combining with HF to form insoluble calcium fluoride, thus preventing the extraction of calcium from tissues and bones.

1.4 Electrophilic Fluorination Reactions

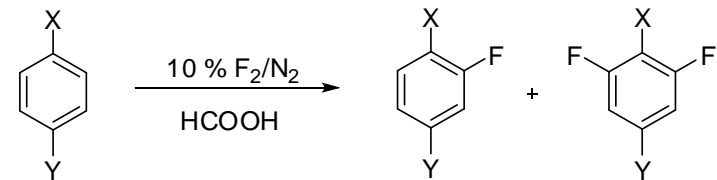
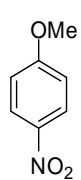
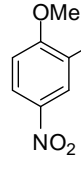
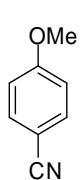
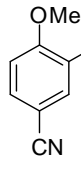
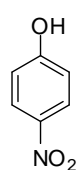
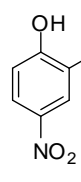
1.4.1 Fluorination of Aromatic Substrates

The electrophilic fluorination of aromatic systems, by transformation of C–H to C–F bonds, has been widely investigated as fluoro-aromatics are useful in the life sciences and are important building blocks in the synthesis of more complex structures. A brief summary of the literature is described here.

1.4.1.1 Fluorination of Aromatic Substrates Bearing Electron-Withdrawing Substituents Using Fluorine Gas

Fluorination of 1,4-disubstituted substrates in acidic reaction media, in which only one position is activated towards electrophilic attack by the presence of appropriately situated electron releasing (OH, OMe, NHAc, Me) and withdrawing (NO₂, CN) group *para* to one another (Table 1), allows the synthesis of a range of mono-fluorinated aromatic systems (**14**, **17**, **20**).²⁵

Table 1: Direct fluorination of deactivated aromatics

 <p>X = OMe, OH Y = NO₂, CN, CHO</p>			
Arene	Conversion/ %	Product	Ratio
 13	87	 14	8:1
 16	82	 17	7:1
 19	67	 20	7:2

When both *para* di-substituted groups are strongly electron withdrawing the aromatic substrate is too unreactive towards electrophilic attack for fluorination to occur.²⁶

Alternatively, it has also been found that aromatic systems which contain two strong electron-withdrawing groups that are in positions *meta* to one another (**22**, **24**), which are highly deactivated towards electrophilic attack, can be fluorinated using acidic reaction media²⁷ (Table 2).

Table 2: Direct fluorination of deactivated aromatics

$\text{X, Y} = \text{NO}_2, \text{CN}$

Arene	Conversion/ %	Product	Yield/ %
<p>22</p>	27	<p>23</p>	94
<p>24</p>	28	<p>25</p>	85

1.4.1.1.1 Fluorination of Aromatic Substrates Bearing Electron-withdrawing Substituents Using Continuous Flow Reactors

The use of continuous flow reactor devices has many advantages for applications in synthetic organic chemistry over standard batch-wise processes as very small quantities of material and solvents can be used when appropriate. There are other benefits which include low manufacturing, operation and maintenance costs and low power consumption. In reactions involving gas and liquids such as direct fluorination, the contact between the reagents is increased immensely because of the large surface area that exists between phases when present in a micro-channel. This leads to improved control, heating or cooling and overall performance of the reactor system.⁶ Continuous flow reactors have been designed by the Durham group (Figure 4)²⁹. The basic, prototype microreactor consists of a solid piece of nickel metal which has a 0.5

mm wide groove etched into its surface. Delivery of fluorine to one end of the reaction chamber (the shallow groove) is controlled by an accurate electronic mass-flow controller and reagents are delivered a short distance downstream *via* a mechanised syringe pump.

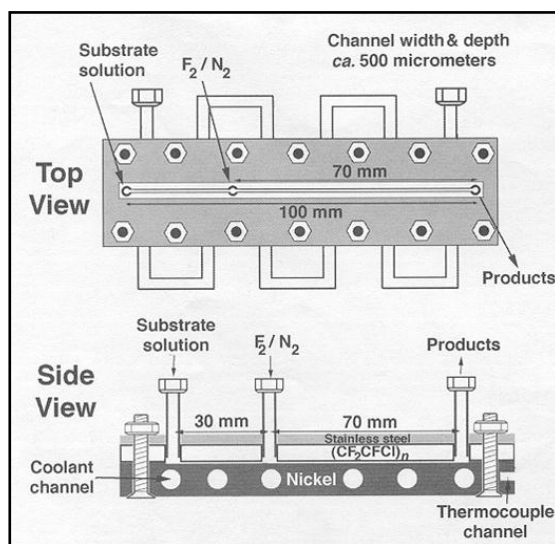


Figure 4: *Single channel microreactor*

The gas and liquid mixtures flow down the micro-channel in a ‘pipe flow’ (Figure 5) manner, whereby a film of the liquid flows across the surface of the micro-channel, with the gas flowing through the centre. This is a major advantage for reactivity because, in these cases, surface area contact between phases is maximised making mixing extremely rapid and reactions diffusion controlled. Pipe-flow is the logical outcome because of the opposing beneficial pressure P of the gas, and the viscous drag on the liquid adhering to the sides of the capillary.²⁹ The alternative possibility is slug flow where alternate ‘slugs’ of gas and liquid follow each other down the reactor channel. This is not as effective for phase mixing compared with pipe flow and is not observed when this flow reactor design is used.

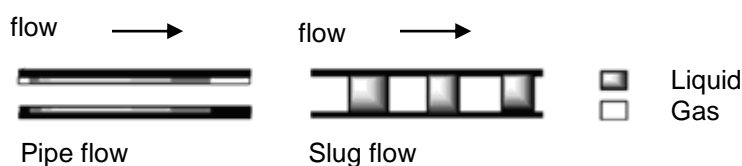
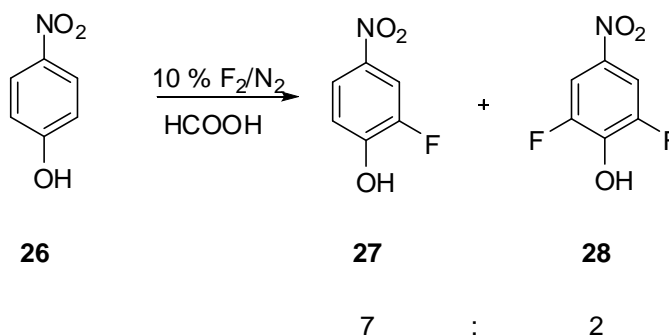


Figure 5: *Pipe and slug flow*

A 30-channel microreactor device has also been designed by the Durham Group. This can be operated continuously for the fluorination of various substrates. In general, the microreactor devices can produce ca. 0.2 g of product per hour per channel therefore, if operated continuously, a two-sided 30-channel device, having a total of 60 channels, would be capable of providing *ca.* 300 g per day. By scale-out, 10 reactors could provide ca. 3 kg of product per day. This shows that flow reactor technology is a realistic method for the bulk fluorination of substrates.²⁸

A variety of continuous flow direct fluorination reactions have been carried out on many substrates including aromatics and 1,3-dicarbonyl compounds. The reactions are carried out using continuous flow techniques by passing fluorine gas at the desired flow rate, diluted to a 10 % mixture in nitrogen, through a microreactor along with the substrate in formic acid solution being added by syringe pump at the desired speed and volume. The product is then collected in a PTFE flask, ready for aqueous work-up.

Direct fluorination reactions of 1,4-disubstituted aromatic systems bearing an electron withdrawing and releasing group, using microreactor technology have previously been investigated³⁵ with the products gained being consistent with an electrophilic substitution process (Scheme 4).



Scheme 4: Fluorination of 4-nitrophenol

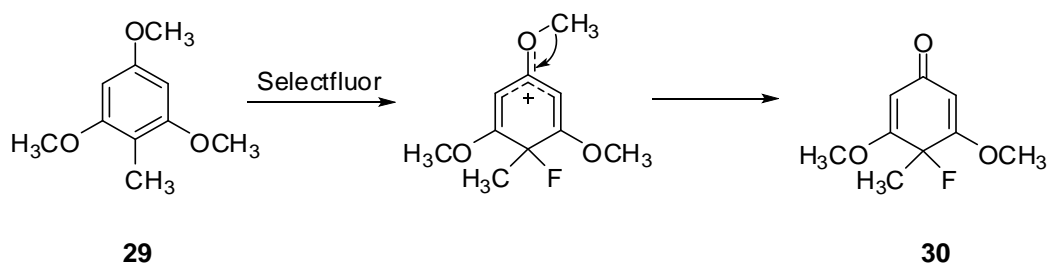
High selectivity and yields of mono-fluorinated products can be obtained using either acetonitrile or formic acid as the solvent.

1.4.1.2 Fluorination of Aromatic Substrates Bearing Electron-donating Substituents

In contrast to fluorination of aromatics bearing electron-withdrawing groups, reactions of aromatic compounds containing electron-donating groups have not been fully investigated. The fluorination of some methoxybenzene, aniline and toluene systems are the few examples of such reactions that have been explored.

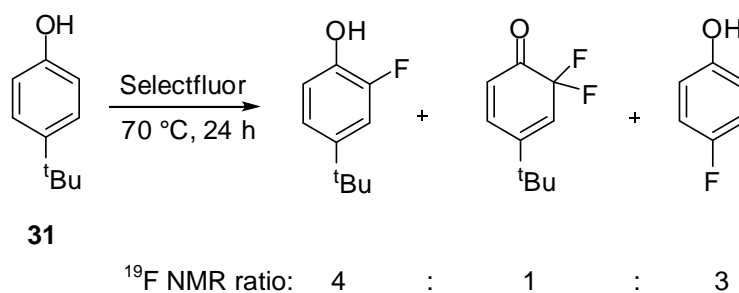
1.4.1.2.1 Fluorination of Aromatics Bearing Electron-donating Substituents Using N-F Compounds

The highly activated aromatic substrate 1,3,5-trimethoxy-2-methylbenzene (**29**) undergoes electrophilic fluorination by Selectfluor™, however, once formed, the fluorinated product readily forms the *para*-quinol type structure (**30**) (Scheme 5).³⁰ 4-Methoxytoluene and 2-methoxynaphthalene can also be converted to 4-fluoro-4-methylcyclohexa-2,5-diene-1-one and 1,1-difluoro-2-oxo-1,2-dihydronaphthalene, respectively, using the same conditions.



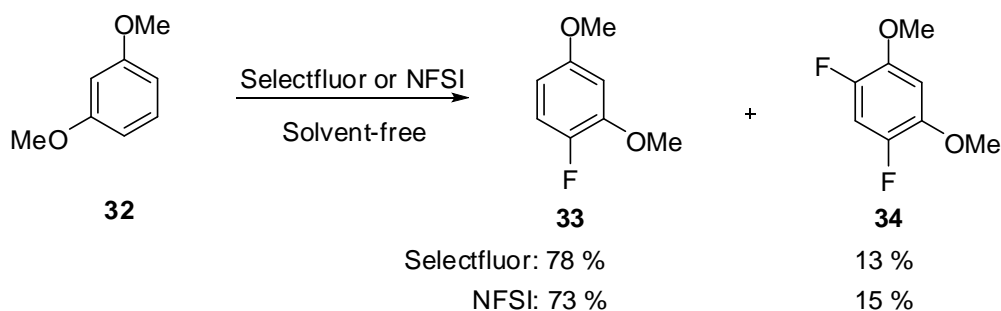
Scheme 5: Fluorination of 1,3,5-trimethoxybenzene with Selectfluor™

Similarly, Stavber³¹ has shown that the analogous *para*-quinols or *para*-quinol ethers are formed exclusively when 2,4,6-trimethylphenol, 2,6-di-*tert*-butyl-4-methylphenol and 4-*tert*-butylphenol (**31**) (Scheme 6) are fluorinated using Selectfluor™. It has also been shown that ionic liquids can also be used as the reaction media to give better selectivity and yield.³²



Scheme 6: Fluorination of substituted phenols

Both SelectfluorTM and NFSI can be used to fluorinate 1,3-dimethoxybenzene (**32**) to give 4-fluoro-1,3-dimethoxybenzene (**33**) and 4,6-difluoro-1,3-dimethoxybenzene (**34**) in high overall yield.³³ The mixture of isomers and remaining starting material, however, make product separation and purification difficult.



Scheme 7: Fluorination of 1,3-dimethoxybenzene

The fluorination of other electron-rich aromatics (**35**, **37**, **40**) using SelectfluorTM, in ionic liquids, is also possible. The yields are comparable, and in some cases are higher, than those obtained in acetonitrile. Although the yields are often poor, good selectivity can be achieved in some examples shown in Table 3.

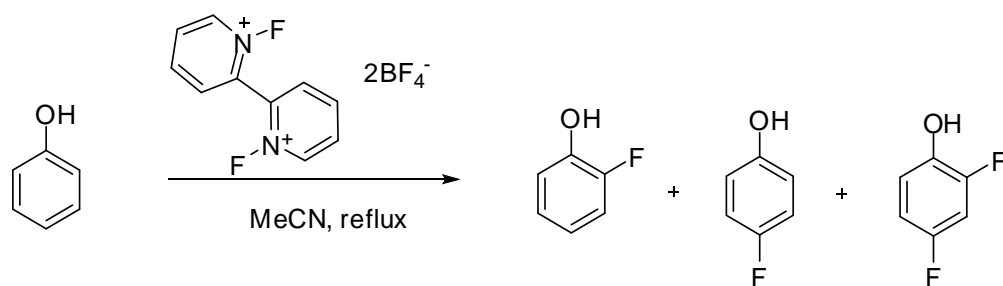
Table 3: Fluorination of electron-rich aromatics using Selectfluor™ in ionic liquids³⁴

c1ccccc1R
 $\xrightarrow[\text{Ionic liquid}]{\text{Selectfluor}}$
Fc1ccccc1R

Arene	Yield/ %	Products	Ratio
 35	51	 36	100
 37	56	 38	93:6
 40	50	 41	95:5
		 42	

N-Fluoropyridinium salts have been used in a range of electrophilic fluorination reactions. *N,N*-Difluorobipyridinium salts, where there are two N–F sites, can also be used in the same way. These have particularly high fluorinating power due to the electron-withdrawing effect of the N–F moieties. The 2,2-isomer was found to be the most potent fluorinating agent and reactions using this reagent can be seen in Table 4.³⁵ The reactions gave average to good yields but with poor selectivity, with both *ortho* and *para* substitution occurring in addition to di-fluorination.

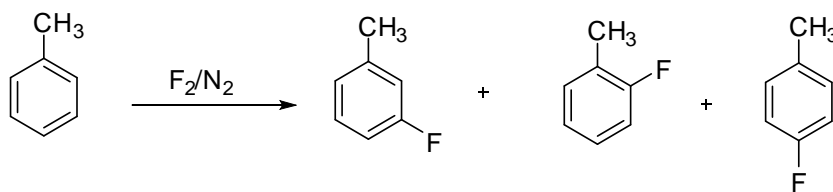
Table 4: Fluorination of electron-rich aromatics using *N,N*-difluorobipyridinium salts



Arene	Product	Yield Ratio/ %
 43		39 (2-F): 33 (4-F): 5 (diF)
 44		40 (2-F): 28 (4-F): 8 (diF)
 45		72 (4-F): 10 (diF): 3 (2-F)
 46		61 (1-F): 18 (diF)

1.4.1.2.2 Direct Fluorination of Electron-rich Aromatic Substrates

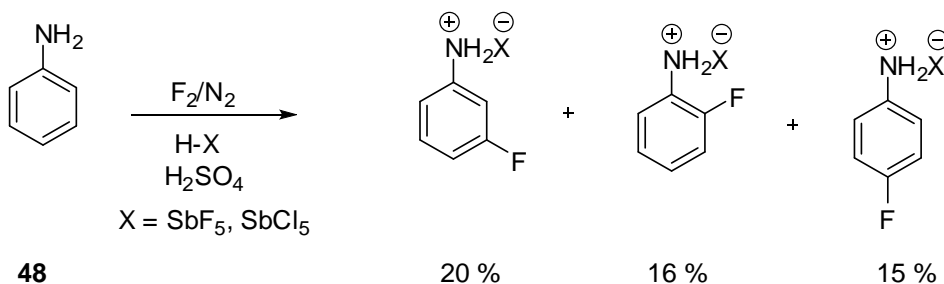
Many workers have attempted to fluorinate toluene (**47**), with limited success. Most recently, Jahnisch *et al*³⁶ have shown it is possible to fluorinate toluene using microreactor technology but the reaction does not go to completion and a mixture of isomers is obtained, with overall yield of fluorinated products only being 41 % (Scheme 8).



47

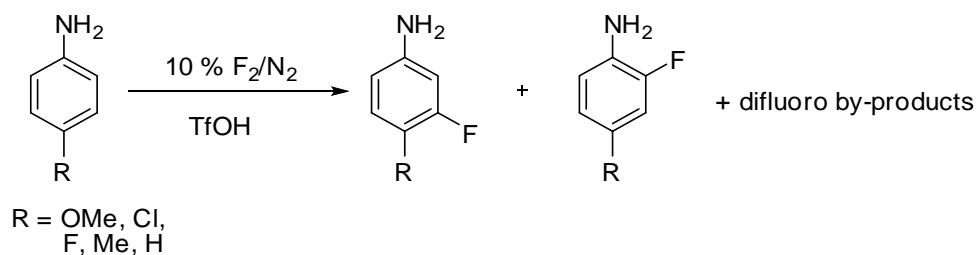
Scheme 8: Direct fluorination of toluene using microreactor technology

Interestingly, the fluorination of aniline (**48**) in strongly acid media results in, mainly, *meta*-fluoroaniline with some *ortho* and *para*-isomers present (Scheme 9). This indicates that aniline is protonated during the reaction to giving the NH_3^+ moiety, which is an inductive electron-withdrawing substituent, favouring *meta* fluorination.



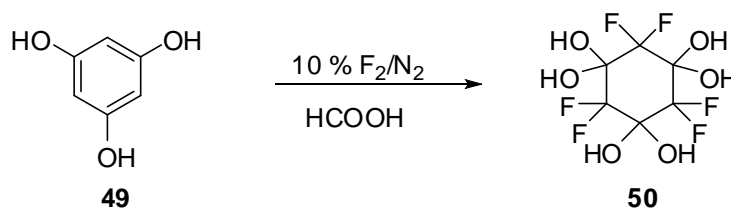
Scheme 9: Direct fluorination of aniline

The same conditions were used to compare the fluorination of different anilines substituted by electron-donating ($\text{R} = \text{OMe}$ and Me) and electron-withdrawing ($\text{R} = \text{F}$ and Cl) groups in the *para*-position (Scheme 10). The selectivity was improved but conversion only reached 60 %. As expected, from the rules governing electrophilic aromatic substitution, conversion of the substrate decreased when the inductive electron-withdrawing power of the substituent increased. However, *meta* regioselectivity, relative to the NH_2 moiety, increased with the conjugative electron-donating power of the substituent.³⁷



Scheme 10: Direct fluorination of substituted anilines

Alternatively, phloroglucinol (**49**) was expected to be too reactive for controlled direct fluorination, however, when this compound was fluorinated the hexafluorohexahydroxy- product (**50**) was obtained (Scheme 11).³⁸

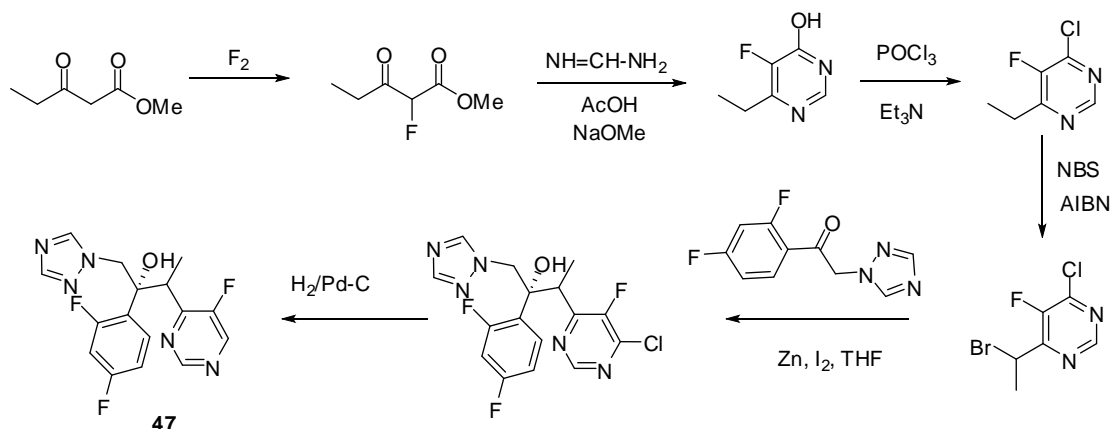


Scheme 11: Direct fluorination of phloroglucinol

These results show that little is known about the fluorination of electron-rich aromatic substrates and that there is scope for more research in this area.

1.5 Synthesis of Fluorinated Heterocycles

Direct fluorination of heterocycles has proven to be very difficult in the past and so building block synthesis strategies using fluorinated 1,3-dicarbonyl systems have been employed, as shown in Scheme 12, in the synthesis of the broad spectrum anti-fungal agent, Voriconazole³⁹ (**47**). Although this building block strategy is useful, there are methods where fluorination of heterocycles has been possible which allow fluorinated molecules to be synthesised in fewer synthetic steps.



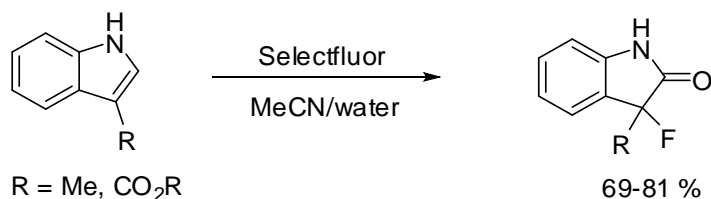
Scheme 12: *Synthesis of Voriconazole*

In addition, there are only a limited number of publications that describe the synthesis of fluorinated 5-membered ring heterocycles due to the lack of appropriate fluorination methodologies for these substrates. The synthesis of fluorinated 6-membered ring heterocycles is now relatively well developed and the methodology involving halogen exchange and fluoro-dediazotisation are the most widely used methods for synthesis of such systems.

This thesis will be concerned with the synthesis of 5-membered heterocyclic systems, specifically pyrazole derivatives and so a survey of the literature concerning electrophilic fluorination of 5-membered ring heterocycles is discussed below.

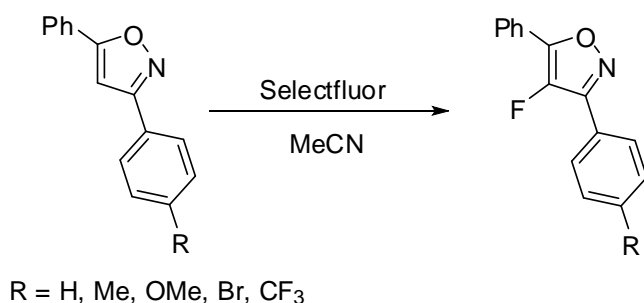
1.5.1 Fluorination of Heterocyclic Systems Using Selectfluor™

A few examples of heterocyclic systems with an electron-donating group in the ring were found to react directly with Selectfluor™ under certain conditions. Reaction of 3-substituted indoles with Selectfluor™ in a mixture of acetonitrile/water gives the 3-fluorooxindole in good yield (Scheme 13).⁴⁰ When water was not added to the reaction mixture, a complex mixture was obtained but a higher yielding reaction is possible when ionic liquids were employed.⁴¹



Scheme 13: Fluorination of indoles

Alternatively, the direct C-4 fluorination of 3,5-diarylisoaxazoles, via electrophilic fluorination with SelectfluorTM has been demonstrated by Stephens (Scheme 14).⁴² This is the first and only example of the selective direct fluorination of isoxaoles.

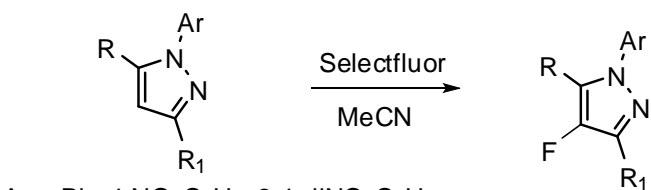
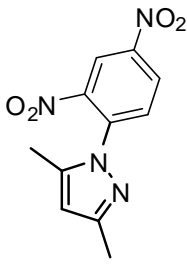
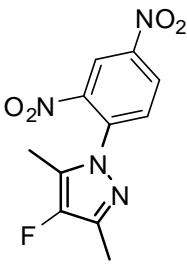
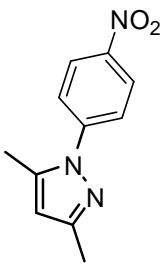
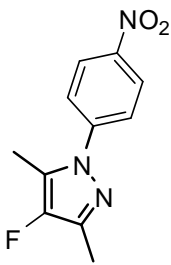
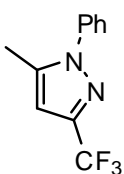
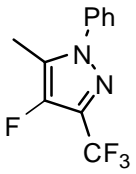


Scheme 14: Fluorination of 3,5-diarylisoxazoles

The conversions of these reactions were poor, even when a large excess of the fluorinating agent was used. It was speculated that a competitive *N*-fluorination of the isoxazole nitrogen⁴³ may be the reason for the incomplete reaction, although this could not be proven. Trace amounts of a polar product, that may have been the *N*-F isoxazole, were often observed by TLC, however attempts to isolate this compound were never successful. Hydrolysis of the *N*-F adduct, however, on TLC or upon work-up would regenerate the starting isoxazole. Although the conversion of these reactions is poor, the reaction still allows the synthesis of some novel 4-fluoro-3,5-diarylisoxazoles.

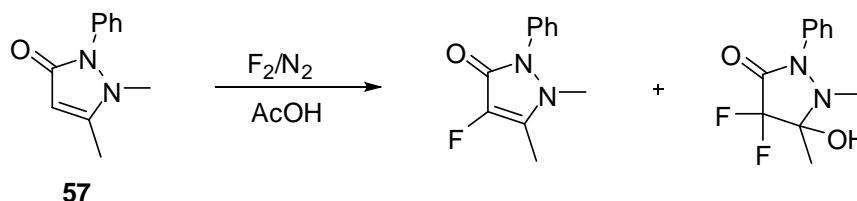
Sloop⁴⁴ also reported that the fluorination of *N*-aryl pyrazoles, where the nitrogen of the ring is protected by an aryl group, could be achieved in a similar manner (Table 5).

Table 5: Fluorination of *N*-aryl pyrazoles

 <p>Ar = Ph, 4-NO₂C₆H₄, 2,4-diNO₂C₆H₃ R/R₁ = Me, Ph, CF₃</p>		
Pyrazole	4-Fluoropyrazole	Yield/ %
 51	 52	30
 53	 54	49
 55	 56	40

1.5.2 Direct Fluorination of Heterocyclic Systems

The fluorination, by elemental fluorine, of antipyrine (**57**) is one of the very few direct fluorination reactions on heterocyclic systems that has been reported (Scheme 15).⁴⁵

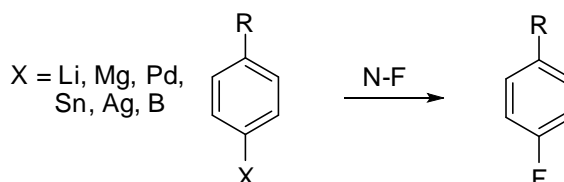


Scheme 15: Direct fluorination of antipyrine

The fluorination of pyrrole systems has also been investigated. Fornarini *et al*⁴⁶ demonstrated that the mono-fluorination of *N*-methylpyrrole gave low yields (0.7–6.2 %) of the desired product, with the main product being polymeric material. No other reactions between 5-membered rings and fluorine have been reported.

1.6 *Ipso* Fluorination of Organometallic and Boronic Acid Aryl Derivatives

As discussed above, electron-rich substituents attached to an aryl ring are often necessary to promote fluorination of aromatic substrates but the yield and conversion varies with the reactivity of the fluorinating agent and substrate in addition to the reaction conditions employed. Also, isomers and products from multiple fluorination of the ring often occurs, which results in an inseparable mixture of fluorinated products. An alternative strategy is to carry out *ipso* fluorination that is displacement of a group on carbon for fluorine, for example boronic acids, silyl ethers and metals are now being used to direct the fluorination of aromatics and make reactions more selective and higher yielding (Scheme 16).



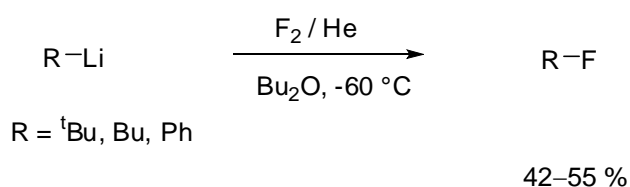
Scheme 16: *Ipso* fluorination reaction

In this thesis the *ipso* fluorination of boronic acids will be investigated to see if fluoro-aromatics could be synthesised in high yield and conversion, with few by-products and so a survey of the literature concerning *ipso* fluorination is included below

1.6.1 Fluorination of Organometallic Aromatic Substrates

1.6.1.1 Group 1 Metal-Mediated Fluorinations

Fluorination of organo-lithium substrates has been shown to be possible when elemental fluorine was used as the electrophilic fluorinating agent. The use of hydrocarbon ether solvents was required as these were unreactive towards fluorine gas at -60 °C. It was found that the HF produced in the fluorination reaction reacted immediately with the organometallic compound to give the corresponding hydrocarbon (hydro-delithiation) as well as the desired arylfluoride (Scheme 17).

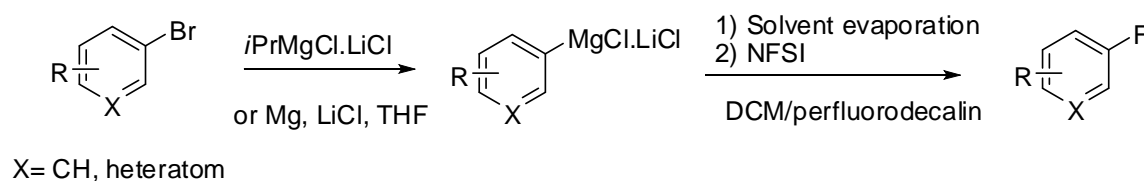


Scheme 17: Fluorination of organo-lithium substrates

Aliphatic organometallic compounds were shown to be more reactive than the aromatic organometallic compounds with these giving higher yields. Although this reaction demonstrates that the *ipso* fluorination of lithium sites is possible, the yields are poor in most cases, a very low temperature is required and the starting organo-lithium compounds are sometimes difficult to handle.⁴⁷

1.6.1.2 Group 2 Metal -Mediated Fluorinations

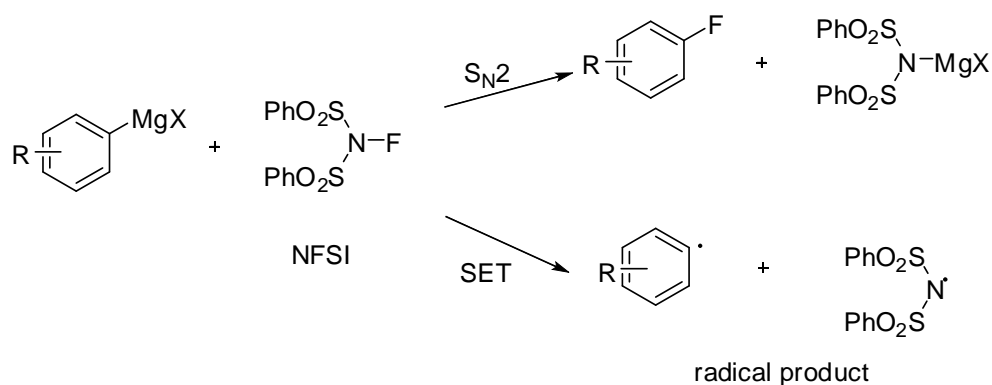
Aryl- and heteroaryl Grignard reagents can be converted to the corresponding fluorinated products by subsequent reaction with an electrophilic fluorination reagent such as NFSI (Scheme 18).⁴⁸



Scheme 18: Fluorination of Grignard reagents

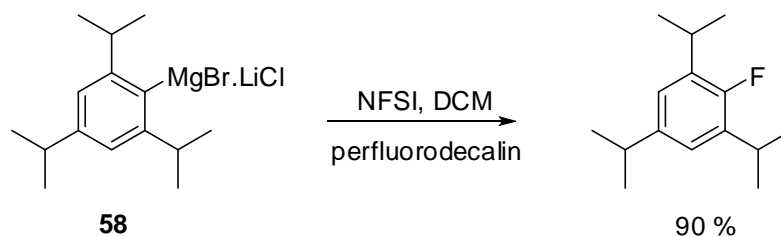
Removal of the THF, after the formation of the organo-magnesium complex, was required and DCM then added to prevent decomposition of the Grignard reagent. A fluorinated co-solvent was also required to prevent abstraction of a proton by the aryl radical formed. The addition of the fluorinated solvent was shown to increase the yield of the fluorinated product by up to 15 %.

This process is believed to proceed by a nucleophilic attack at the fluorine atom of NFSI (S_N2 mechanism), which competes with single electron transfer (SET) procedures, leading to radical intermediates. Thus, the formation of the protonated arene as a side product can be attributed to the formation of a radical intermediate, which abstracts a hydrogen atom from the solvent (Scheme 19).



Scheme 19: Reaction pathways of the fluorination of Grignard reagents

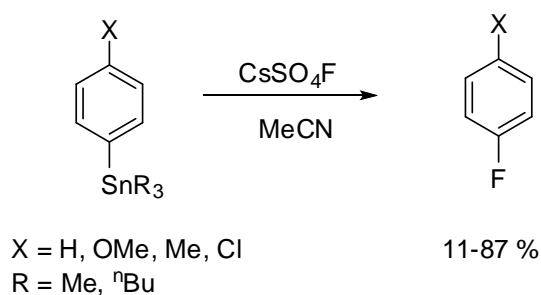
Both aromatic and heterocyclic systems can be fluorinated, in good to high yield, using this magnesium-mediated process, although low temperatures and multiple steps involving evaporation and re-addition of solvents, are required to obtain the arylfluoride. The yields are highest when there was significant steric hindrance at the magnesium site, with the highest yield achieved when the 2,4,6-triisopropylphenyl derivative (**58**) was fluorinated (Scheme 20).



Scheme 20: Representative fluorination of organo-magnesium complexes

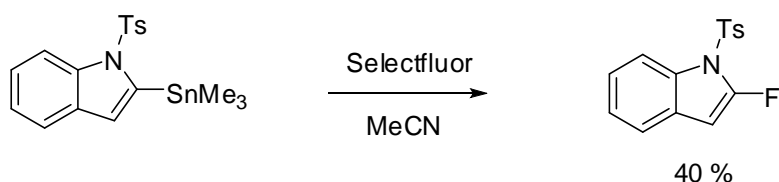
1.6.1.3 Fluorination of Aryl Stannanes

Chambers demonstrated that the *ipso* fluorination of aryl stannanes was possible using caesium fluoroxy sulfate (Scheme 21). The yields were good, particularly when R = Me, with no difluorinated products being detected.



Scheme 21: Fluoro-destannylation of arylstannanes by caesium fluoroxy sulfate (CFS)

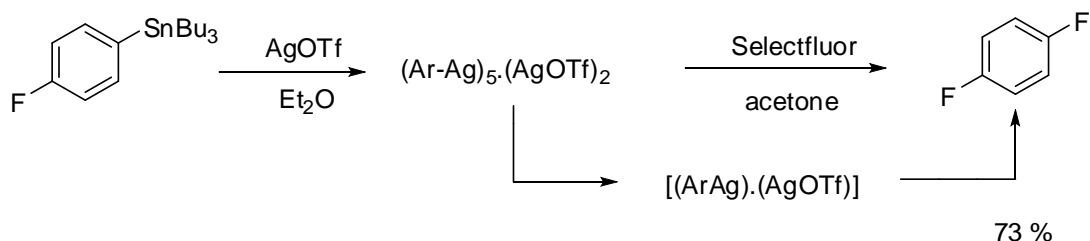
Similarly, it has been shown that *ipso* fluorination of heterocyclic stannanes using Selectfluor™ is possible (Scheme 22), although it was found that hydro-destannylation and di-fluorination occurs as well as the desired fluorination.⁴⁹



Scheme 22: Fluoro-destannylation of stannylindoles by Selectfluor

1.6.1.3.1 Silver-Mediated Fluorination of Arylstannanes

Alternatively, Ritter has shown that silver intermediates can be used to mediate the fluorination of arylstannanes to greatly improve the fluoro-destannylation reaction (Scheme 23). The fluorination is functional group tolerant, high yielding, has rapid reaction times and is a relatively easy reaction to perform, although arylstannanes are highly toxic and so this is not a viable transformation in life-science discovery applications. Another disadvantage of this reaction is the quantity of hydro-destannylated by-products afforded (10–20 %).



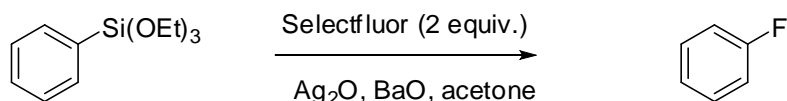
Scheme 23: Fluoro-destannylation of arylstannanes using SelectfluorTM

Ritter suggests that the silver mediated carbon-fluorine bond formation involves bimetallic oxidation-reductive elimination. Reductive elimination could proceed *via* one-electron redox participation of two silver atoms. Although, high valent aryl silver fluoride intermediates were not observed, the yield of fluorinated products was not affected upon addition of radical scavengers, suggesting that the formation of free radical intermediates is less likely.⁵⁰

1.6.1.4 Metal Mediated Fluorination of Aryltrialkoxysilanes

1.6.1.4.1 Silver-Mediated Fluorination of Aryltrialkoxysilanes

Aryltrialkoxysilanes and SelectfluorTM react in the presence of Ag₂O to give functionalised aryl fluorides (Scheme 24).⁵¹ Conversely to arylstannanes, aryl silanes are low in toxicity, inexpensive, and are stable to a variety of reaction conditions although not all are stable towards chromatography.



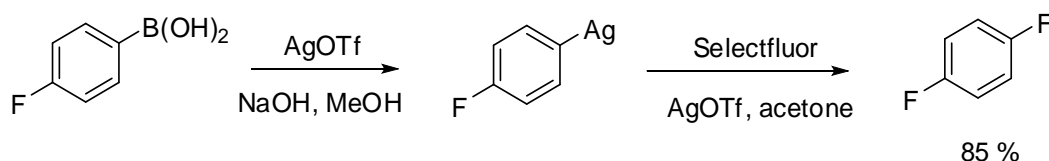
Scheme 24: Fluorination of aryltrialkoxysilanes using *Selectfluor*TM

Ag(I) oxide (two equivalents) was required to afford the high yields of the fluorinated product. Ag₂O is easy to handle, straightforward to remove by filtration, and less expensive than other silver salts. The fluorination reaction does not proceed without the presence of the silver salt but can be carried out in water, although acetone is the superior solvent. Again, by-products resulting from C–H instead of C–F bond formation are observed. Proto-desilylation can be avoided by addition of barium oxide which is thought to sequester silicon-based Lewis acids formed during the reaction and, therefore, reduce by-product formation and increase the yield of fluorinated product. Indeed, addition of one equivalent of BaO increased the yield by up to 10 %. It has also been demonstrated that the fluorination of arylsilanes can be achieved using XeF₂ as the fluorinating agent, with Pyrex as a catalyst.⁵²

1.6.1.5 Metal Mediated Fluorination of Arylboronic Acids

1.6.1.5.1 Silver-Mediated Fluorination of Arylboronic Acids

The fluorination of arylboronic acids *via* an aryl silver moiety has also been reported by Ritter as an alternative to fluorination of arylstannane derivatives (Scheme 25).⁵³ Boronic acids are more stable and considerably less toxic than arylstannanes, are commercially available and much more easily prepared. The fluorination reactions are less efficient than with arylstannanes and so a base must be added to promote the reaction.

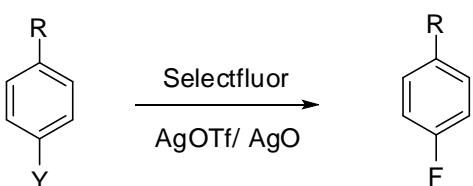


Scheme 25: Fluorination of boronic acids using silver salts and *Selectfluor*TM

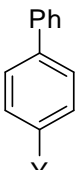
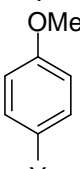
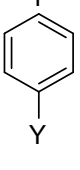
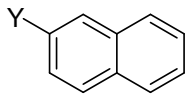
Molecular sieves can also be added to the reaction vessel to reduce phenol production, due to the presence of water. The by-products resulting from C–H instead of C–F bond formation, found in the fluorination of arylstannanes, were not observed in the fluorination of boronic acids.

Table 6 shows that *ipso* fluorination of electron-rich arylstannanes, -silanes and boronic acids using silver salts is an effective method for the synthesis of arylfluorides with high yields achieved in all cases. Although these are effective reactions, they require expensive silver salts and, particularly in the cases of the arylstannanes, the starting materials also have to be pre-synthesised and purified.

Table 6: Comparison of the *ipso* fluorination reactions of Ar-Y ($Y = \text{Sn}(\text{Bu})_3, \text{B}(\text{OH})_2, \text{Si}(\text{OEt})_3$) mediated by silver salts^{50, 53, 51}



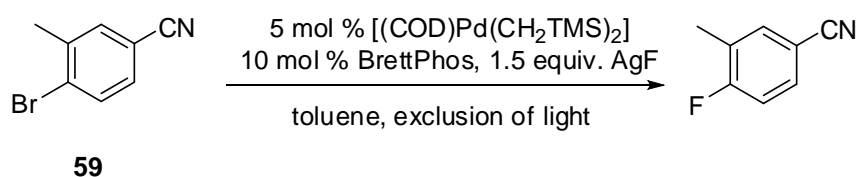
Y = $\text{Sn}(\text{Bu})_3, \text{B}(\text{OH})_2, \text{Si}(\text{OEt})_3$

Ar-Y	Y	Yield/ %
	$\text{Sn}(\text{Bu})_3$	83
	$\text{B}(\text{OH})_2$	82
	$\text{Si}(\text{OEt})_3$	83
	$\text{Sn}(\text{Bu})_3$	76
	$\text{B}(\text{OH})_2$	84
	$\text{Si}(\text{OEt})_3$	76
	$\text{Sn}(\text{Bu})_3$	82
	$\text{B}(\text{OH})_2$	82
	$\text{Si}(\text{OEt})_3$	90
	$\text{Sn}(\text{Bu})_3$	79
	$\text{B}(\text{OH})_2$	75
	$\text{Si}(\text{OEt})_3$	60

1.6.1.6 Palladium Mediated Fluorination

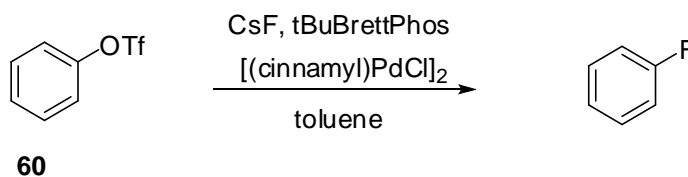
Current work in the field of synthesis of arylfluorides has focused on using palladium complexes to promote the fluorination of arylbromides, aryltriflates and arylboronic acids. Palladium catalysis has been successfully employed in several carbon–heteroatom bond formations, including carbon–fluorine bonds.⁵⁴

Buchwald *et al*⁵⁵ showed that selective fluorination of arylbromides (**59**) and triflates (**60**) was possible with a nucleophilic fluoride source and palladium complexes. The initial investigations of fluorination of C–Br bonds demonstrated that Pd complexes, aided by the ligand BrettPhos (2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl and dicyclohexyl-[3,6-dimethoxy-2-(2,4,6-triisopropylphenyl)phenyl] phosphane), can promote the conversion of an arylbromide to an arylfluoride. However, the scope of aryl bromides that can be fluorinated is limited to electron-deficient substrates bearing an *ortho* substituent (Scheme 26).



Scheme 26: Fluorination of arylbromides using nucleophilic AgF

Conversely, *ipso* fluorination of aryltriflates, also reported by Buchwald, are much more general (Scheme 27)⁵⁵. Simple aromatic substrates can react rapidly to provide aryl fluorides in high yield. Hindered substrates such as 4-acetyl-2,6-dimethylphenyl triflate and heterocyclic systems were also fluorinated successfully.

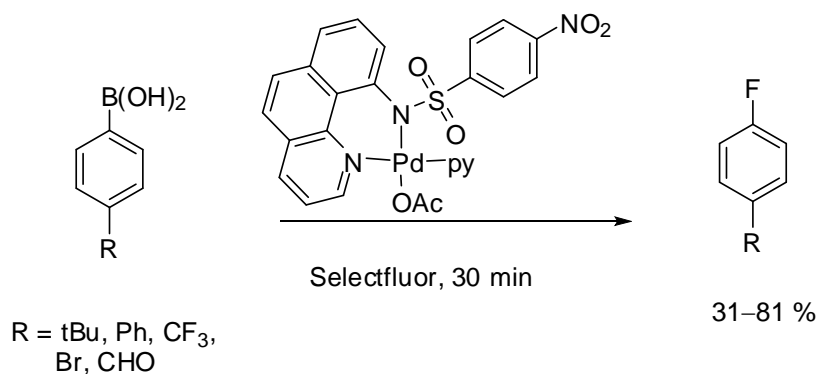


Scheme 27: Fluorination of aryltriflates using nucleophilic AgF

Basic groups, such as amines or carbonyls, in the *ortho* position of the aryltriflate, however, are not tolerated and no reaction occurs. This is thought to be because the basic group coordinates the Pd centre, possibly preventing transmetalation. The reaction is also very sensitive to water, with the CsF having to be dried at 200 °C.

1.6.1.6.1 Palladium Mediated Fluorination of Arylboronic Acids

Alternatively, Ritter has shown that it is possible to fluorinate boronic acids mediated by various palladium complexes to afford the desired arylfluoride in good yield with the fluorination reaction tolerating a wide variety of functional groups (Scheme 28).

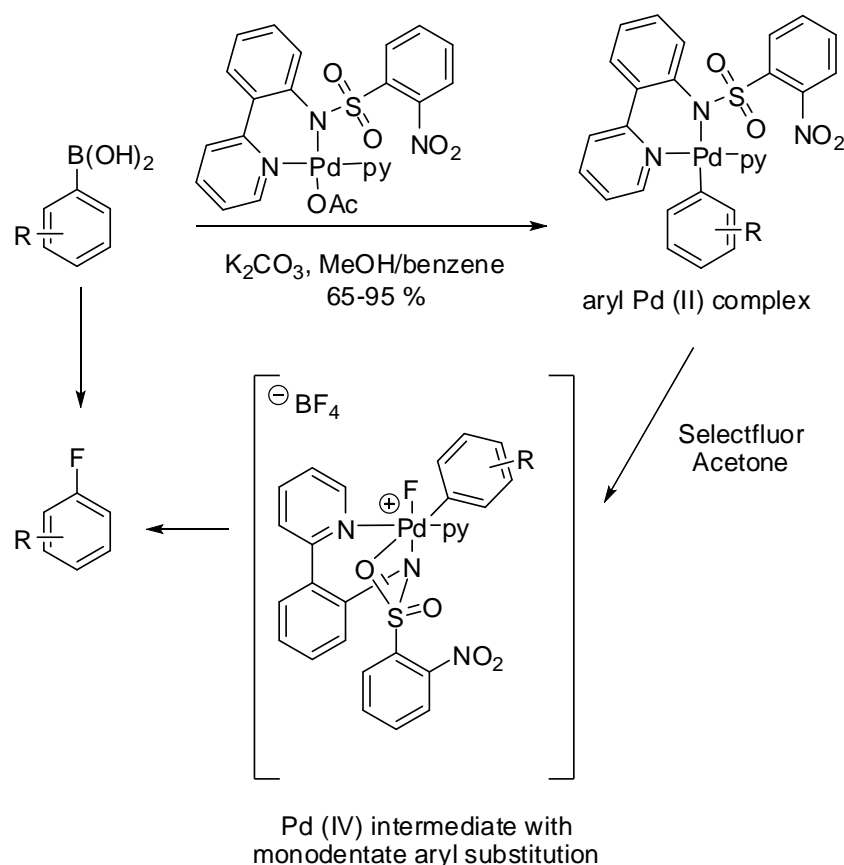


Scheme 28: Fluorination of boronic acids using palladium complexes and Selectfluor™

Although fluorination reactions involving palladium complexes have been shown to be effective in the synthesis of arylfluorides, they do require difficult and expensive synthesis to the palladium complex with one equivalent of palladium complex required for each reaction.

Two possible mechanisms for the fluorination reaction have been suggested: electrophilic palladium–carbon bond cleavage or carbon–fluorine reductive elimination from a discrete, high-valent palladium fluoride. It is thought that the redox activity of Pd (II) may be important for the fluorination to proceed, which suggests a high-valent, discrete palladium fluoride complex as an intermediate before carbon–fluorine reductive elimination.⁵⁶ Ritter has also proposed that the pyridyl-sulfonamide ligand may play an important role in the C–F bond formation. It was thought the ability of the pyridyl-

sulfonamide ligand to function as a bidentate-tridentate-bidentate coordinating ligand during oxidation and reductive elimination, combined with the appropriate electronic requirements of the sulfonamide to position the aryl substituent trans to the sulfonamide ligand in the Pd(II) complex and the fluoride ligand trans to the sulfonamide ligand in the Pd(IV) complex, may be the reason for facile C–F bond formation (Scheme 29).⁵⁷

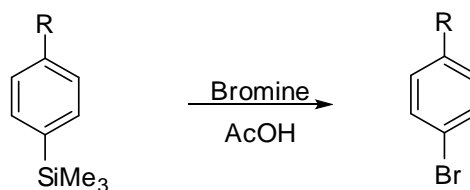


Scheme 29: *Proposed mechanism of palladium catalysed fluorination of boronic acids*

1.6.2 Metal-free Fluorination of Aromatic Substrates

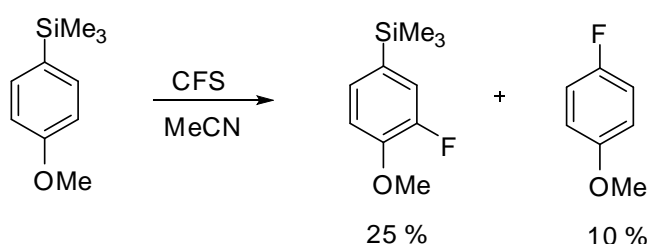
1.6.2.1 Metal-free Fluorination of Aryltrialkoxysilanes

Eaborn^{58, 59} has reported that the bromo-desilylation reaction, to obtain arylbromides, using elemental bromine is possible (Scheme 30). It was shown that the bromination reaction favoured electron-rich substituents in the 4-position and indicated that steric effects may have an influence on the reaction rate, with the order of the rate of reaction being $R = \text{Me} > \text{Et} > {}^i\text{Pr} > {}^t\text{Bu}$.



Scheme 30: Bromo-desilylation of arylsilanes

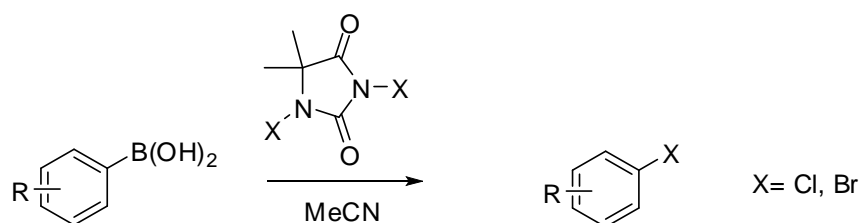
Similarly, the *ipso* fluoro-desilylation of trialkylsilyl- derivatives has been reported using XeF₂⁶⁰ and caesium fluoroxysulfate (CsSO₄F/CFS)⁶¹ (Scheme 31). In the case of the reactions using CFS, fluorination as well as fluoro-desilylation occurred.



Scheme 31: Fluoro-desilylation of arylsilanes

1.6.2.2 Metal-free Fluorination of Arylboronic Acids

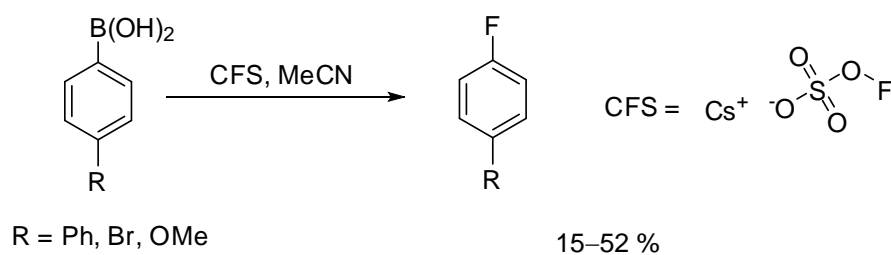
Halo-deboronation reactions using electrophilic halogenating agents, without the need for a metal, have been reported using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) and 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) (Scheme 32). The desired halogenated product can be synthesised in good to excellent yield and the reaction tolerates a range of functional groups.



Scheme 32: Halogenation of arylboronic acids using DBDMH and DCDMH

Only when a strong electron-donating group was present did electrophilic aromatic halogenation compete with *ipso* displacement of boron. Interestingly, addition of a catalytic amount of base increased the yield of the product.⁶² This shows that the halogenation reaction is possible with N–X halogenating agents and indicates that it may be possible when using similar N–F electrophilic fluorinating agents.

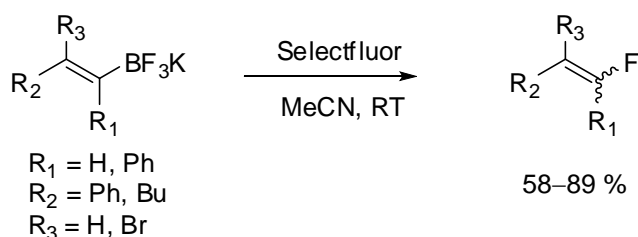
Previous work by Widdowson⁶¹ has shown that caesium fluoroxysulfate (CFS), in acetonitrile, can convert boronic acids to their fluoro-derivative (Scheme 33). For example, reaction of 4-methoxyphenylboronic acid with CFS gave 4-fluoroanisole as the major product in 30 % yield. Replacement of boron was, therefore, shown to occur at a faster rate than that of hydrogen on this activated, electron rich, substrate.



Scheme 33: Fluoro-deboronation using caesium fluoroxysulfate

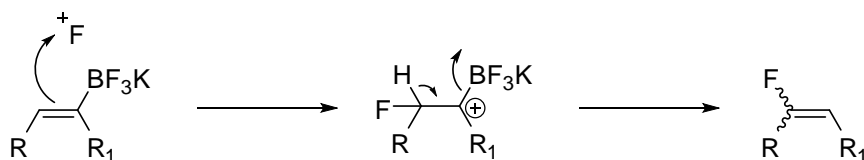
Widdowson also demonstrated that it was possible to carry out fluoro-deboronation on less activated substrates such as biphenylboronic acid and 1-naphthylboronic acid but the yields were always less than 30 %. This shows that caesium fluoroxysulfate is not very reactive towards boronic acids and is also a poor choice of fluorinating agent due to its explosive nature.

Prakash⁶³ demonstrated that the fluorination of alkenyl boronic acids and trifluoroborate salts was possible with Selectfluor (Scheme 34). The reaction proceeded in high yield but with no regio-selectivity, with a 50:50 E/Z ratio being obtained in most cases.



Scheme 34: Fluorination of alkenyl trifluoroborate salts with Selectfluor

The mechanism is thought to proceed *via* an addition-elimination reaction *via* a carbocation intermediate since both isomers are formed and the reaction was faster with the more highly nucleophilic trifluoroborate derivative, compared to the boronic acid (Scheme 35).



Scheme 35: Proposed addition-elimination mechanism

In 2009, it was reported that the fluorination of boronic acids, using SelectfluorTM, was possible without the presence of a metal catalyst.⁶⁴ A range of aromatic systems were fluorinated efficiently (**61–64**), although proto-deboronated products were obtained as well as the desired arylfluoride (Table 7). This is the first metal-free electrophilic fluorination process of boronic acid and trifluoroborate derivatives to afford arylfluorides with SelectfluorTM. Interestingly, no product was isolated when the boronic acid was in the *meta*-position. Lemaire also discovered that the boronic acid gave higher yielding reactions than the trifluoroborate derivative, conversely to Prakash's findings in the fluorination of alkenyl boronic acids and trifluoroborates (Scheme 34).

Table 7: Metal-free fluorination of arylboronic acids using Selectfluor™

Boronic Acid	Ar-F (GC)/ %	Ar-H (GC)/ %
	90	0
	75	12
	100	0
	67	33

1.7 Conclusion

The fluorination reactions of aromatics bearing both electron-withdrawing and electron-donating substituents have been reported to proceed well, with excellent selectivity and yield achieved. Alternatively, the fluorination of electron-rich aromatics is not efficient and gives a mixture of inseparable fluorinated isomers and oxidative products.

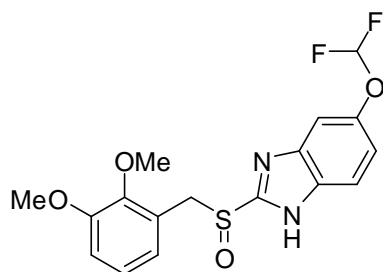
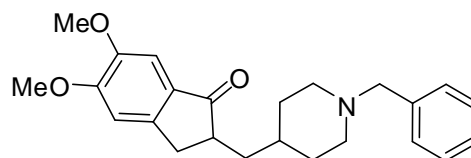
Limited work has been carried out on the fluorination of 5-membered heterocycles, although the fluorination of indoles, pyrazoles and isoxazoles has been reported in a few cases, with low yields of the desired products often obtained.

The *ipso* fluorination reaction has been shown to be an effective method for the isolation of arylfluorides, including electron-rich aryl compounds which are difficult to fluorinate selectively. High yields can be achieved when lithium, magnesium, tin, silicon and boron *ipso* sites are fluorinated. The addition of silver and palladium can also improve the efficiency of the fluorination at tin, silicon and boron sites. Metal-free processes have also been shown to be efficient, with high yields being achieved, particularly in the fluorination of electron-rich boronic acids using Selectfluor. Proto-deboronation is a major problem in all fluorination reactions involving *ipso* substitution at the boron/silyl/stannyl site, in both metal-free and metal-mediated processes.

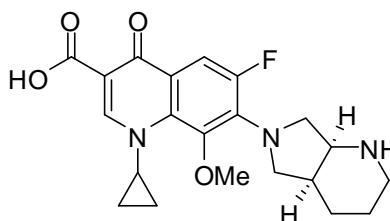
Direct Fluorination of Electron-rich Aromatic Systems

2.1 Introduction

Aromatic systems bearing electron-donating substituents, including dimethoxybenzene derivatives can be found in many drug molecules including Protonix (**65**) (Wyeth), a proton pump inhibitor used to treat oesophagus inflammation, and Aricept (**66**) (Eisai), a cholinesterase inhibitor used to treat Alzheimer's disease.

**65****66**

Very few top selling drugs contain aromatic rings with both a fluorine atom and several electron-donating substituents due to very few efficient methods for their synthesis. Avelox⁶⁵ (**67**) (Bayer AG) is one of the few, recent, top selling drugs to contain, both a methoxy- and fluorine substituent on the same ring.

**67**

Other important electron-donating aromatic structures found in drugs include benzodioxane derivatives.

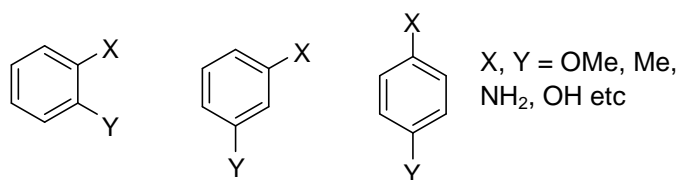


Figure 6: 1,2, 1,3 and 1,4 di-substituted aromatics bearing 2 electron-donating systems for fluorination studies

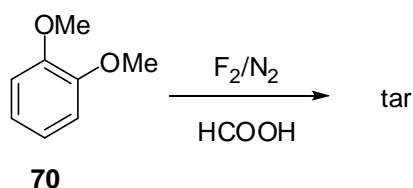
The direct fluorination reactions will be carried out using both batch and flow methodologies. The main aim of this chapter is to discover whether these reactions can be controlled in any way, and if so, whether products can be isolated and purified to further expand the use of direct fluorination techniques for applications in the life-science industries.

2.3 Results and Discussion

2.3.1 Direct Fluorination of Electron-rich Aromatics

2.3.1.1 Direct Fluorination of 1,2-Dimethoxybenzene

Batch fluorination of 1,2-dimethoxybenzene (**65**) using 10 % F₂/N₂, in formic acid, gave a dark brown reaction mixture which gave a dark brown solid after aqueous work-up (Scheme 36).



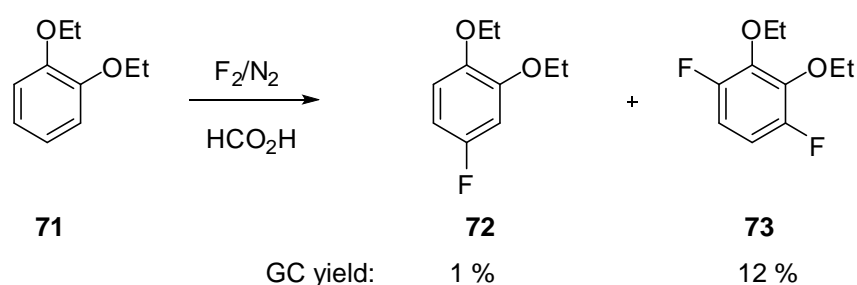
Scheme 36: Fluorination of 1,2-dimethoxybenzene

The ¹⁹F NMR spectrum of the crude material did not show any significant fluorine signals and GC-MS did not give identifiable products. The reaction was repeated at -10 °C, using an external ice bath. It was hoped that cooling the reaction would reduce any side reactions occurring and prevent tar formation, however, the product was still very complex and again no fluorinated product could be observed. The solvent was then changed to acetonitrile to see if this aided the fluorination but again, no fluorination of

70 occurred with black tar being the major product. The reaction was repeated in the flow reactor but again only tar was obtained.

2.3.1.2 Direct Fluorination of 1,2-Diethoxybenzene

Similarly, fluorination of 1,3-diethoxybenzene (**71**) (Scheme 17) gave a significant amount of tar produced, however there was some evidence of fluorination by ^{19}F NMR spectroscopy (Figure 7). The tar was removed by passing the product mixture through a silica plug and the crude material analysed.



Scheme 37: Fluorination of 1,2-diethoxybenzene

The ^1H NMR spectrum of the crude product showed that there was still a large proportion of starting material remaining. GC-MS showed that 81 % starting material remained and that two other products were present with $m/z = 184.0$ and 201.7 which were thought to correspond to 1,2-diethoxy-4-fluorobenzene (**72**) ($\delta_{\text{F}} = -130$ ppm) and 2,3-diethoxy-1,4-difluorobenzene (**73**) ($\delta_{\text{F}} = -121$ ppm) consistent with ^{19}F NMR data.

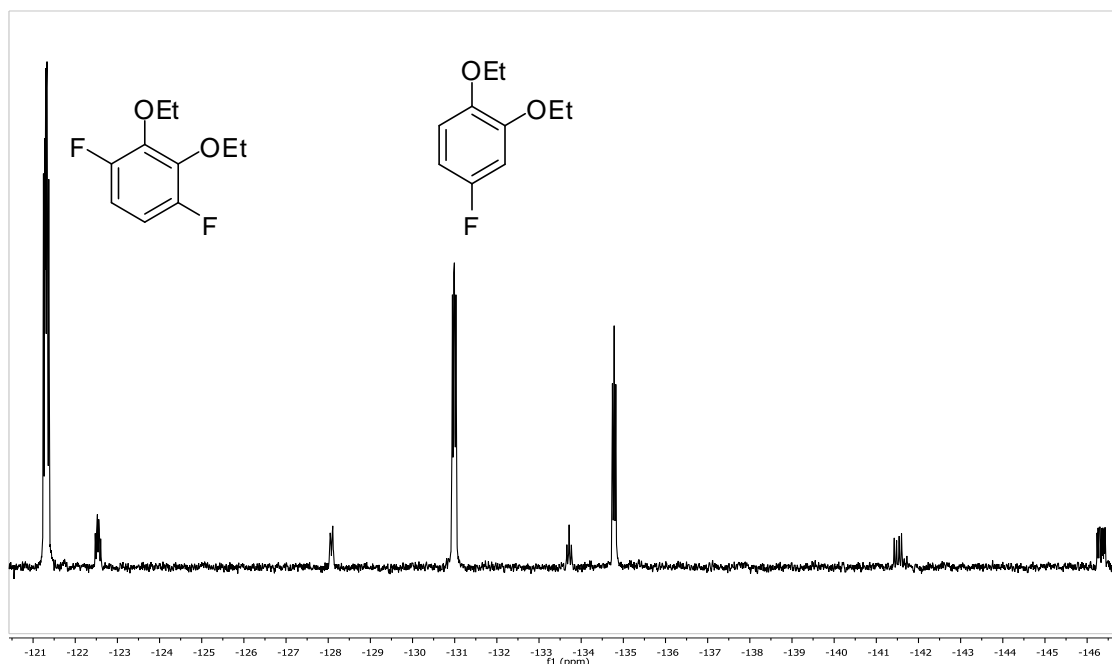
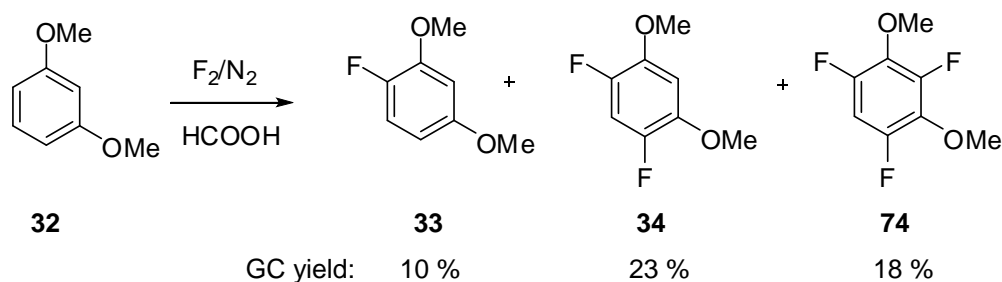


Figure 7: ^{19}F NMR spectrum from the fluorination of 1,2-diethoxybenzene

The reaction was repeated with a higher rate of fluorine addition (20 mL/ min) but this just resulted in more tar being produced, with no increase in the yield of the fluorinated products. Although this reaction afforded some fluorinated products, the reaction gave very poor conversion and similarly, the comparative reaction in the flow reactor did not improve the conversion of the reaction. These results show that 1,2-dialkoxybenzenes are too reactive or oxidatively unstable towards elemental fluorine and so 1,3-dialkoxy substrates were investigated.

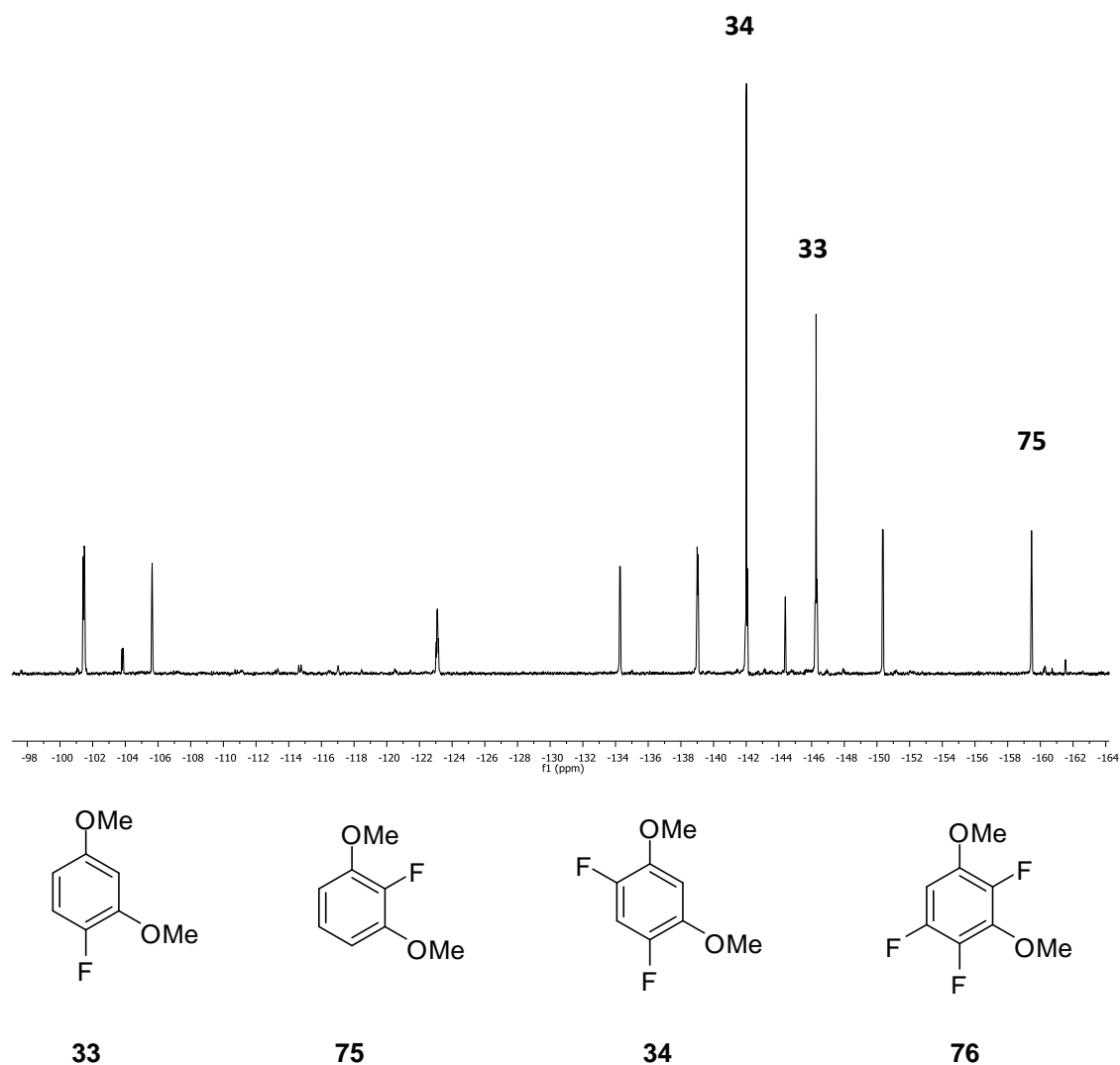
2.3.1.3 Direct Fluorination of 1,3-Dimethoxybenzene

The reaction of 1,3-dimethoxybenzene (**32**) and fluorine gave a yellow reaction mixture and after work up, the crude product was a yellow viscous liquid.



Scheme 38: Fluorination of 1,3-dimethoxybenzene

GC-MS indicated that **33** ($m/z = 156$), **34** ($m/z = 174$) and **74** ($m/z = 192$), had probably been formed, with 40 % of **32** remaining. The ^{19}F NMR spectrum confirmed (Figure 9) that a range of fluorinated products had been obtained, with the major product (35 %) being **34** with 20 % of **32** remaining. Some products could be identified by their shift in the ^{19}F NMR spectrum, on comparison with the literature data.



Literature Values:

-146.5⁶⁶ -159.1⁶⁷ -142.0⁶⁶ -141.2, -156.7, -163.4⁶⁶

Figure 8: ^{19}F NMR shifts from fluorination of 1,3-dimethoxybenzene

It was thought that using the flow reactor for the fluorination reaction may reduce the number of products obtained and make the reaction more selective. The reaction was

therefore repeated, using a mechanised syringe pump for the addition of the substrate at the rate 1 mL/min, dissolved in formic acid (5 mL). Fluorine was added at the rate of 15 mL/min and the temperature maintained at 5 °C. It can be seen, in the ^{19}F NMR spectrum (Figure 9) that using the flow reactor can reduce the number of fluorinated products obtained, with the main product (50 %) being **74** although many other products still remained and full conversion from the starting material could not be achieved.

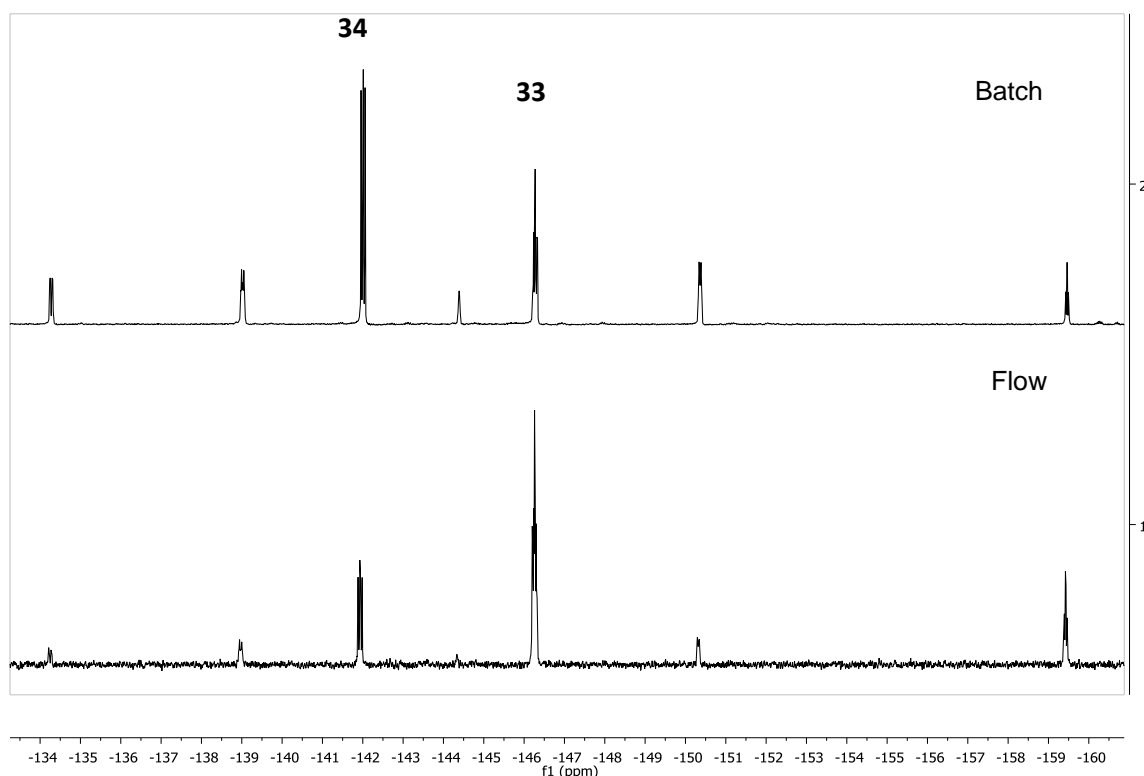
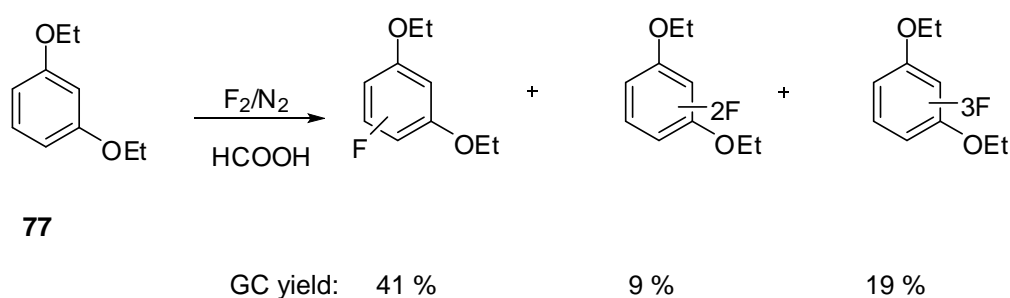


Figure 9: ^{19}F NMR spectrum comparing the batch and flow reaction

A range of reaction conditions, including higher and lower rates of addition of fluorine and the substrate, did not improve the conversion. Pure fluorinated products could not be isolated from the mixture due to the difficulties in separation by column chromatography and the complex mixtures of products formed in all reactions attempted.

2.3.1.4 Direct Fluorination of 1,3-Diethoxybenzene

Similarly, the fluorination of 1,3-diethoxybenzene (**77**) gave a mixture of products with $m/z = 184$, $m/z = 202$ and $m/z = 220$ which correspond to mono-, di- and tri-fluorinated products (Scheme 39).



Scheme 39: Fluorination of 1,3-diethoxybenzene

The aromatic region of the ^1H NMR spectrum (Figure 10) shows that a mixture of products had been obtained. Again the mixture of products could not be separated and so a large excess of fluorine was used to see if this improved the conversion but this only increased the amount of tar produced in the reaction, without improving the yield of fluorinated products.

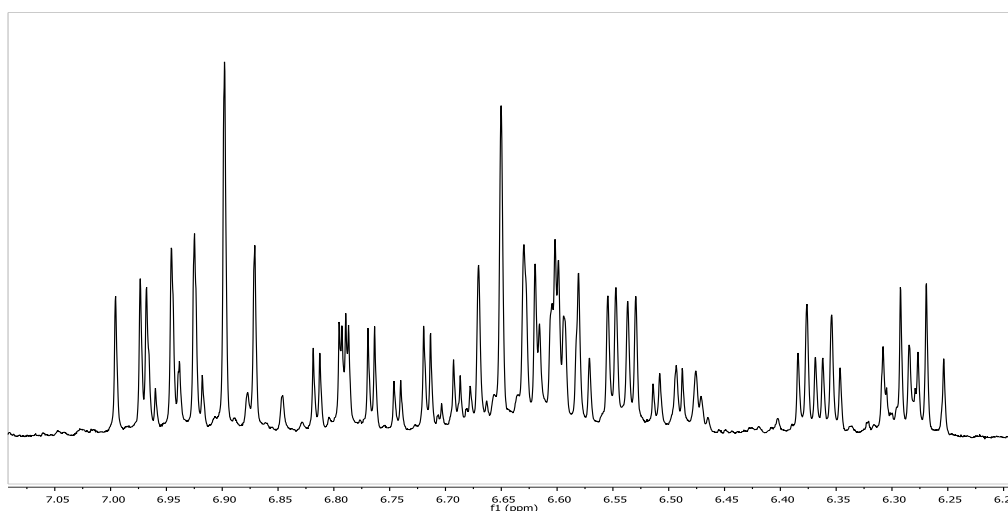


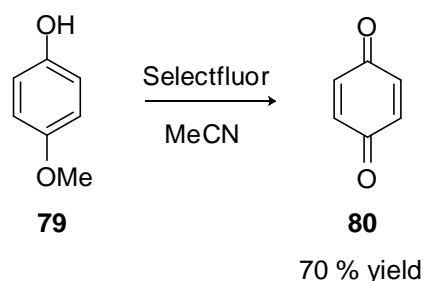
Figure 10: ^1H NMR Spectrum from fluorination of 1,3-diethoxybenzene

These reactions show that 1,3-dialkoxybenzenes are also unsuitable substrates for direct fluorination using elemental fluorine as a mixture of several products is obtained, with

poor yields being observed in all cases when both the batch and flow methods were used.

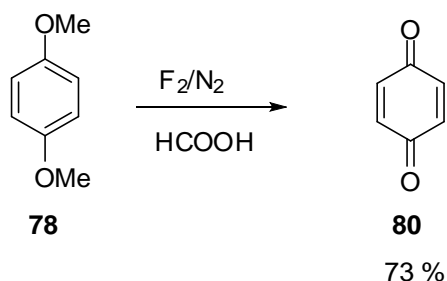
2.3.1.5 Direct Fluorination of 1,4-Dimethoxybenzene

To complete the series of fluorinations, 1,4-dimethoxybenzene (**78**) was attempted (scheme 41), since similar reactions with Selectfluor™ have been shown to give a greater mixture of products including oxidative and fluorinated products (Scheme 40). The oxidative demethylation of 4-methoxyphenol (**79**) by Selectfluor has been shown to give *p*-benzoquinone (**80**), in acetonitrile.⁶⁸



Scheme 40: Demethylation of 4-methoxyphenol

The batch fluorination reaction of **83** and fluorine in formic acid also gave the oxidised product, **82**, in 73 % isolated yield with no evidence of fluorinated products. When the flow reactor was used as a comparison, the conversion reached 75 %. When the solvent was changed to acetonitrile no products could be identified by NMR or mass-spectroscopy. This indicates that an acid must be present to promote the oxidation reaction.



Scheme 41: De-methylation of 1,4-dimethoxybenzene

^1H NMR spectroscopy showed the disappearance of the methoxy- signal at 3.83 ppm with the appearance of a singlet at 6.6 ppm (Figure 11) and ^{19}F NMR spectroscopy showed no fluorinated products had been obtained. GC-MS also showed a mass of $m/z = 108$ consistent with the quinone product, **80**.

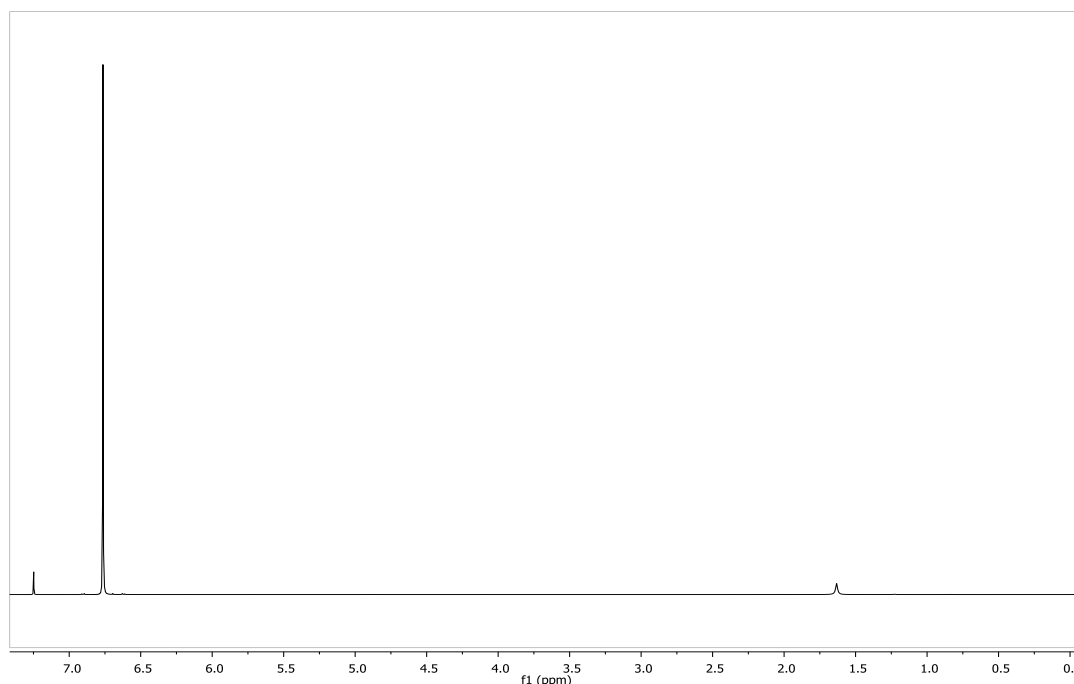
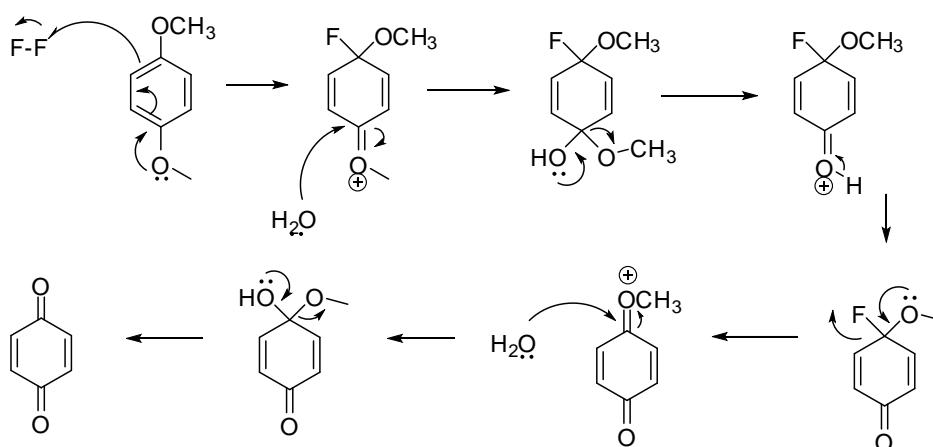


Figure 11: ^1H NMR Spectrum of **78** from fluorination of 1,4-diethoxybenzene

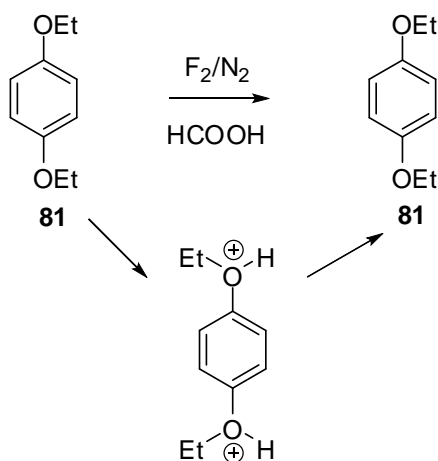
Fluorine is not only useful as an electrophilic fluorinating agent, but as an efficient oxidising agent and the proposed mechanism for the oxidation by fluorine and water is shown in Scheme 42.



Scheme 42: Proposed mechanism of oxidation to the p-benzoquinone

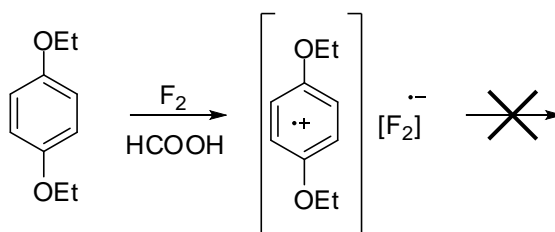
2.3.1.6 Direct Fluorination of 1,4-Diethoxybenzene

1,4-Diethoxybenzene (**81**) was expected to be much less easily oxidised due to the larger and less labile ethoxy- group. After reaction with fluorine and work-up, starting material was recovered. This is a surprising result as one would expect some kind of reaction, either oxidation or fluorination, since the substrate was in a reactive mixture for ~18 h. A possible explanation is that the formic acid protonates the oxygen which makes the ethoxy- groups electron withdrawing and deactivates the system towards electrophilic attack (Scheme 43) although we would expect the same observation in the dimethoxy- system.



Scheme 43: Possible mechanism for the protonation of ethoxy- groups

Alternatively, it is possible that the mechanism involves an electron transfer process as shown in Scheme 44, where the intermediate is very stable and resistant to electrophilic attack.



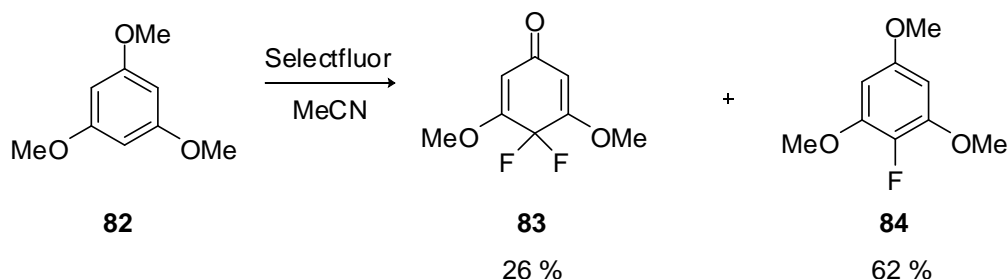
Scheme 44: Alternative mechanism involving a stable radical cation

The electron transfer process assumes the initial formation of a charge-transfer complex between an electron-rich organic molecule and an electron-deficient fluorinating

reagent, followed by one-electron transfer, which forms a cation radical as the active intermediate and precursor of fluorinated or non-fluorinated products.³¹ Reactions involving mesitylene have also given no fluorinated products and a similar mechanism was suggested.²⁶

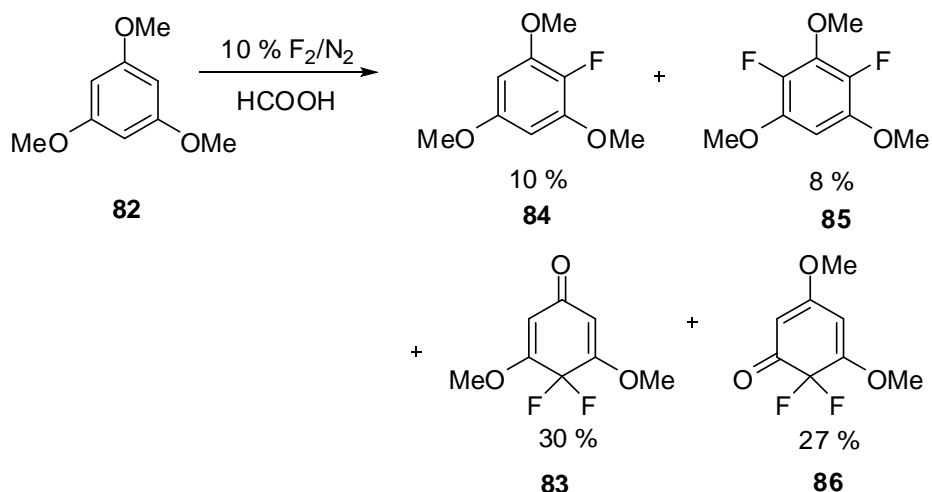
2.3.1.7 Direct Fluorination of 1,3,5-Trimethoxybenzene

Banks³⁰ demonstrated that fluorination of 1,3,5-trimethoxybenzene (**82**), with Selectfluor, gives the 4,4-difluoro-3,5-dimethoxycyclohexa-2,5-dienone (**83**) and 2-fluoro-1,3,5-trimethoxybenzene (**84**), with oxidation and fluorination both occurring, as shown in Scheme 45.



Scheme 45: Fluorination of 1,3,5-trimethoxybenzene with Selectfluor

We confirmed this reaction and, subsequently, direct fluorination was carried out to see if similar results occurred (Scheme 46). The direct fluorination of **82** afforded both fluorinated and oxidised products, with 75 % conversion from the starting material achieved. Although several products were identified by ¹⁹F NMR spectroscopy and GC-MS, the fluorinated products (**84**, **85**) could be easily separated from the oxidised products, **83** and **86**, by column chromatography. However, **84** and **85** could not be separated from one another.



Scheme 46: Direct fluorination of 1,3,5-trimethoxybenzene

On repeating the reaction using the flow reactor, the conversion was improved to 80 %. X-ray crystallography was used to prove the structure of **83** (Figure 12), while other products were identified by comparison with the literature data.³⁰

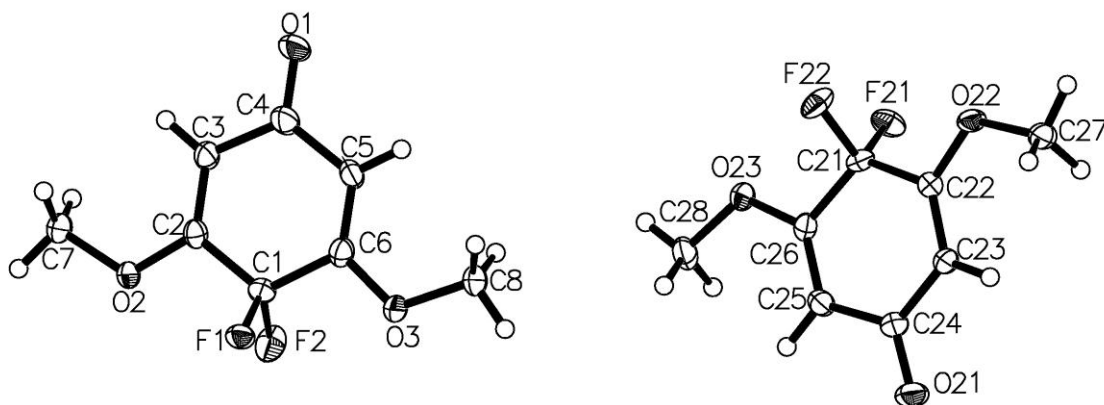


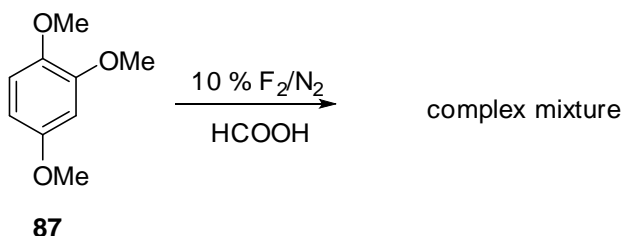
Figure 12: X-ray Crystal Structure of 4,4-difluoro-3,5-dimethoxycyclohexa-2,5-dienone (**83**)

This result shows that direct fluorination can be a useful tool in the synthesis of pharmaceutically relevant molecules, and pure products can be isolated. Other trimethoxybenzene isomers were fluorinated to see if other fluorinated or oxidised products can be isolated in a similar manner.

2.3.1.8 Direct Fluorination of 1,2,4-Trimethoxybenzene

The reaction of fluorine and **78** gave the quinone product, **80**, and **82** gave both fluorinated and oxidised products. To extend this, a reaction of 1,2,4-trimethoxybenzene (**87**) was explored.

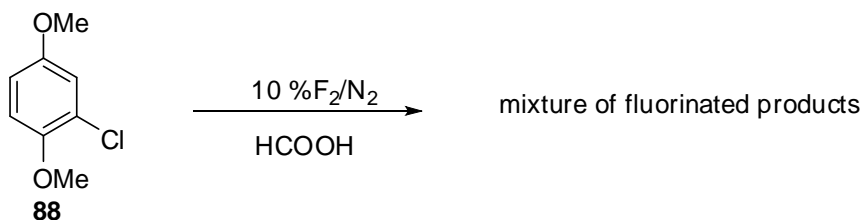
The direct fluorination of **87**, in formic acid, gave a dark brown reaction mixture which consisted of mainly tar, with no significant signals in the ^{19}F NMR spectrum or mass spectrum (Scheme 47). This is possibly due to two methoxy- substituents being *ortho* to one another which is similar to the structure of 1,2-dimethoxybenzene (**70**).



Scheme 47: Direct fluorination of 1,2,4-trimethoxybenzene

2.3.1.9 Direct Fluorination of 2-Chloro-1,4-dimethoxybenzene

It was decided that other substrates with alternative substituents, as well as methoxy-groups, should be investigated as these may change the reactivity of the ring to promote the fluorination reaction and hinder oxidation. It was expected that conversion of the substrate would be decreased when the inductive electron-withdrawing power of the substituent was increased.



Scheme 48: Fluorination of 2-chloro-1,4-dimethoxybenzene

After the fluorination of 2-chloro-1,4-dimethoxybenzene (**88**) was complete, the ^{19}F NMR (Figure 13) and ^1H NMR spectra showed many signals. The reaction mixture was also black, which suggested significant tar formation. As expected due to the addition of the inductive electron-withdrawing chlorine, the conversion was even lower than previous reactions, with starting material being the main peak (92 %) observed in the GC-MS.

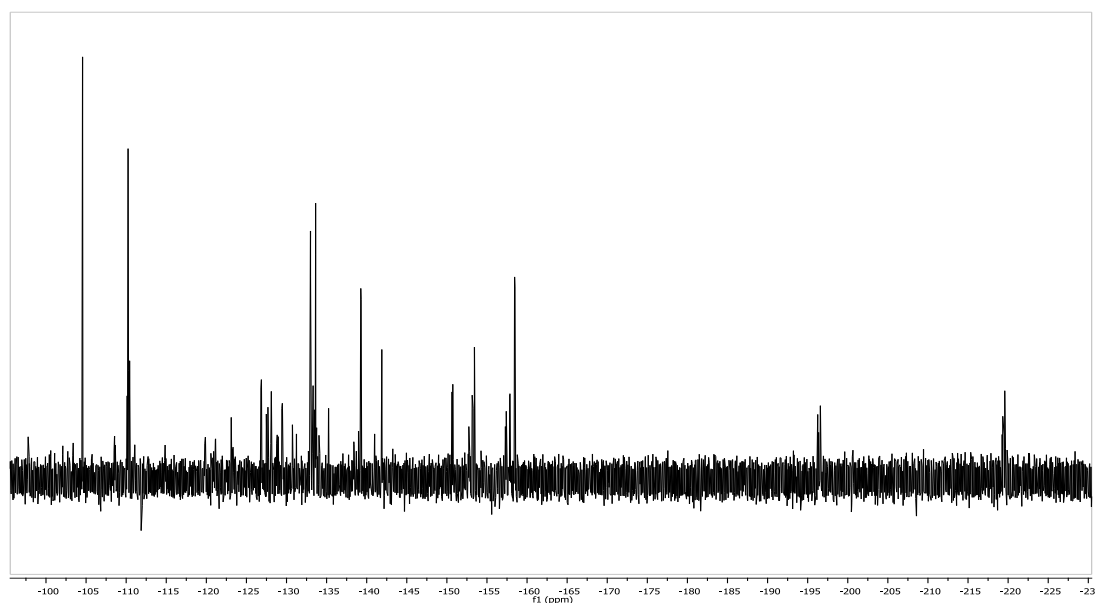


Figure 13: ^{19}F NMR spectrum from fluorination of 2-chloro-1,4-dimethoxybenzene

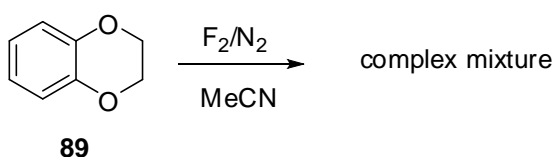
After this result, no further investigations of dimethoxybenzene systems were attempted.

2.3.2 Direct Fluorination of Benzo-1,4-dioxane Systems

As previously mentioned, benzodioxane systems are frequently found in drug molecules. Fluorinated benzo-1,4-dioxanes, therefore, could be studied to get a range of potentially useful drug building blocks. Benzo-1,4-dioxane (**89**) is a derivative of **70** and so it is expected that tar may be produced in the reaction but it was hoped that fluorinated products may be isolated.

2.3.2.1 Direct Fluorination of Benzo-1,4-dioxane

The reaction of **89** with elemental fluorine was carried out using both formic acid and acetonitrile as reaction media (Scheme 49). After aqueous work-up, the crude product was an orange viscous liquid with the ^1H NMR spectrum showing a complex mixture and ^{19}F NMR spectrum showing no signals. It was thought that ring cleavage may have occurred, resulting in breakdown of the molecule. Attempts were made to identify any intermediates from molecule breakdown, but no products could be identified by mass spectroscopy.

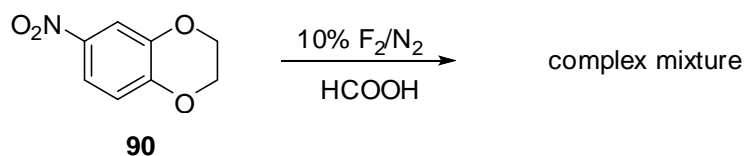


Scheme 49: Fluorination of benzo-1,4-dioxane

Since the fluorination of **89** resulted in a complex mixture, a more deactivated derivative was synthesised to see if this could promote a controlled fluorination reaction.

2.3.2.2 Direct Fluorination of 6-Nitro-1,4-benzodioxane

The reaction was carried out as above, with 6-nitro-benzo-1,4-dioxane (**90**) being dissolved in acetonitrile and formic acid. After aqueous work-up, the crude product was a dark brown viscous material which was sparingly soluble in organic media and found to be mostly tar.

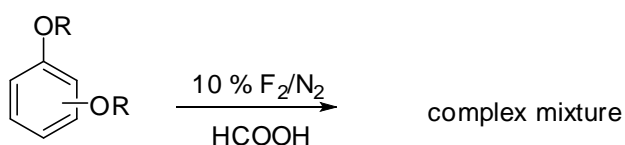


Scheme 50: Fluorination of 6-nitro-benzo-1,4-dioxane

With the data available it was difficult to determine the products gained. Repeated reactions did not give any desired products by NMR or mass spectroscopic analysis and so it was concluded that the direct fluorination of benzodioxane systems is not possible, under the conditions employed.

2.4 Conclusions

This chapter has shown that direct fluorination of electron-rich, highly activated aromatics, affords complex mixtures of products, with multiple fluorinated and oxidised products, and tar being obtained. In most cases isolation of pure products was difficult and usually not attempted. Conversion of the reactions was also poor, with starting material remaining in all cases, making purification even more challenging.



Scheme 51: *Fluorination of electron-rich aromatics*

In the case of the direct fluorination of **78** and **82**, oxidative products could be isolated and separated from the fluorinated products.

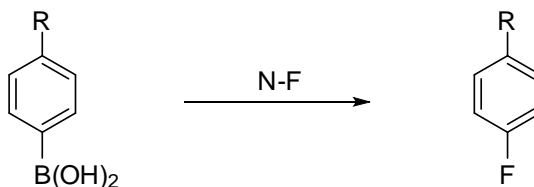
Alternative methods were required to achieve selective and high yielding fluorination of highly activated, electron-rich aromatics. Research turned to exploring the *ipso*-fluorination of aromatics and this will be addressed in Chapter 3.

*Ips*o Fluoro-deboronation of Aryl Boronic Acid Derivatives

3.1 Introduction

As discussed in previous chapters, it is difficult to add fluorine selectively to electron-rich systems with poor yields frequently being obtained. As an alternative strategy, boronic acids could be selectively fluorinated at the *ipso* position then this would allow late-stage fluorination of aromatic substrates and thus allow the facile synthesis of electron-rich fluoro-aromatic substrates.

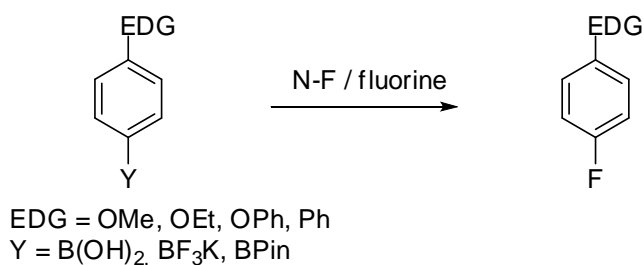
As mentioned in Chapter 1, Lemaire⁶⁴ reported the first metal-free electrophilic fluorination process of boronic acid and trifluoroborate precursors to afford fluoroaryl and fluoroalkyl derivatives in good yield (Scheme 52). Lemaire showed that it is possible to fluorinate naphthyl-, *t*-butylphenyl- and benzyloxyphenylboronic acid systems efficiently but other aromatic systems were not investigated.



Scheme 52: *Ips*o fluoro-deboronation reaction

3.2 Aims and Objectives

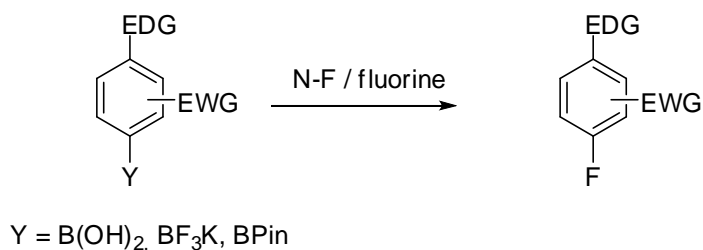
The aim of this chapter is to develop effective methodology for the fluorination of a range of electron-rich arylboronic acid systems similar to the electron-rich aromatics investigated in Chapter 2. It is hoped that the fluoro-deboronation reactions will allow isolation of the desired, mono-fluorinated product in good yield (Scheme 53).



Scheme 53: Fluoro-deboronation of boronic acids containing electron-rich substituents

Although much of the current research on fluoro-deboronation reaction is of boronic acids, a range of trifluoroborate salts, synthesised from their corresponding boronic acids, will also be investigated as they tend to be more reactive and less vulnerable to competing proto-deboronation reactions. The fluorination of the boronic acid and trifluoroborate salts will be compared, to see which derivative is the best for the *ipso* fluoro-deboronation reaction. Boronic acids and trifluoroborate salts will be fluorinated with a range of fluorinating agents such as Selectfluor™, *N*-fluoropyridinium salts and elemental fluorine, to see what the best general conditions are for fluorination of arylboronic acid derivatives.

Arylboronic acids containing one electron-withdrawing substituent and one electron-donating substituent and electron-deficient arylboronic acids will also be fluorinated to determine the scope of the fluorination process (Scheme 54).



Scheme 54: Fluoro-deboronation of aromatics containing electron-donating and electron-withdrawing substituents

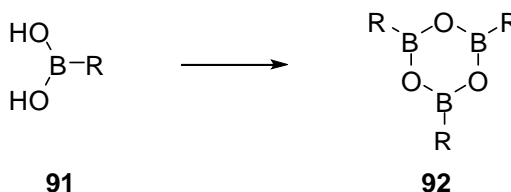
Heterocyclic boronic acids will also be investigated as no research has been carried out into the fluorination of heterocyclic boronic acids and this would be a potentially very efficient method for the synthesis of selectively fluorinated heterocycles.

3.3 Results and Discussion

3.3.1 Synthesis of Trifluoroborate Salts

Prakash⁶³ demonstrated that trifluoroborate derivatives undergo fluoro-deboronation very efficiently. Trifluoroborate salts and boronate esters are known to be more stable with respect to decomposition and so these can often be used as an alternative to boronic acids.

Boronic acids and borate esters were obtained from commercial suppliers whilst trifluoroborate salts were synthesised from literature procedures.⁶⁹ Boronic acids (**91**) are known to decompose to the boroxine trimer (**92**) and although boronic acids can be recrystallised from water, on drying they frequently convert back to the boroxine (Scheme 55).



Scheme 55: *Decomposition of boronic acids to boroxines*

Boroxines (1,3,5,2,4,6-trioxatriborinanes, $\text{R}_3\text{B}_3\text{O}_3$) are six-membered cyclo-trimeric anhydrides of organo-boronic acids which are the most stable forms of R–BO polymers which are formed from the simple dehydration of boronic acids.⁷⁰

A range of trifluoroborate salts were synthesised from their corresponding boronic acid or boronate ester using the literature procedure. 3.3 Equivalents of potassium hydrogen fluoride (KHF_2) are required to fully convert the boronic acid to the trifluoroborate salt.⁷¹

Table 8: Reaction of phenylboronic acids with KHF_2

$ \begin{array}{c} \text{B(OH)}_2 \\ \\ \text{R} - \text{C}_6\text{H}_4 \end{array} \xrightarrow[\text{KHF}_2 \text{ (aq)}]{\text{MeOH}} \begin{array}{c} \text{BF}_3\text{K} \\ \\ \text{R} - \text{C}_6\text{H}_4 \end{array} $					
R-B(OH) ₂	R-BF ₃ K	Yield/ %	R-B(OH) ₂	R-BF ₃ K	Yield/ %
		88			70
		90			69
		91			66
		89			76
		90			74
		92			89
		85			92
		90			88
		70			89
		73			88

Table 8 shows the isolated yields of the potassium trifluoroborate salts synthesised. In all cases the conversion and isolated yields were good to excellent with up to 95 % yield being obtained. All products were white solids which could be purified by multiple

dissolutions in acetone and subsequent filtration to remove any unreacted KHF_2 . The yields were lower with the dimethoxy- derivatives as these were less soluble in methanol and acetone and, therefore, purification proved more difficult. ^{11}B NMR spectroscopy was carried out at each stage to ensure the complete conversion from the boronic acid to the desired potassium trifluoroborate salt. The melting point was also recorded to confirm the trifluoroborate identity as the melting point of the potassium trifluoroborate salt is known to be significantly higher than that of the boronic acid.

3.3.2 Fluoro-deboronation of Electron-rich Arylboronic Acid Systems

3.3.2.1 Fluoro-deboronation of Naphthalene-1-boronic Acid Derivatives

Table 9: Fluoro-deboronation of naphthyl boronic acid derivatives

Y = BPin, B(OH)₂, BF₃K

Boronic Acid	Ar-F: Ar-H ¹	Conversion ² / %	Isolated Yield of 94/ %
<p>93</p>	5:1	47	31
<p>61</p>	1:4	30	25
<p>95</p>	20:1	85	70

¹ Ar-F:Ar-H ratio measured by GC-MS, ²conversion measured by ^1H NMR Spectroscopy

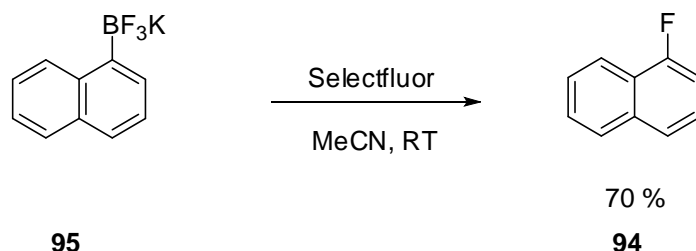
Lemaire⁶⁴ showed that it was possible to fluorinate naphthalene boronic acids (90 % conversion) and trifluoroborate salts (79 % conversion to Ar-F, 21 % to Ar-H) with SelectfluorTM and so this reaction was repeated, using the literature conditions, with the

boronic acid (**61**), pinacol ester (BPin) (**93**) and trifluoroborate salt (**95**) to investigate the reactivity of each system. It was predicated that the trifluoroborate would be the most reactive, with the boronate ester being the least reactive. A summary of the results can be seen in Table 9.

Fluorination of **93** was investigated first as this is the most stable derivative but, resulted in multiple fluorinated products formed in 47 % conversion by NMR spectroscopy. It was decided that a more activated boronic acid was required and so the boronic acid and trifluoroborate derivatives were used.

The boronic acid, **61**, was not very soluble in MeCN at room temperature and so the reaction was heated to reflux to allow the reaction to proceed. After 24 h, **61** had not fully reacted. After a further 6 h, with no change in the conversion, the reaction was worked up. The crude product was shown to be mostly proto-deboronated product, by GC-MS, with unreacted **61** also remaining. This shows that, ideally, the substrate should be soluble in MeCN at room temperature, as heating promotes the unwanted proto-deboronation reaction.

Fluorination of **95** with SelectfluorTM at room temperature (Scheme 56), however, proceeded well with the desired mono-fluorinated product, **94**, isolated in 70 % yield with a multiplet at δ_F -124 ppm in the ^{19}F NMR spectrum. Side products (5 %) were also seen in the ^{19}F NMR spectrum, which were found to be the difluorinated product by GC-MS.

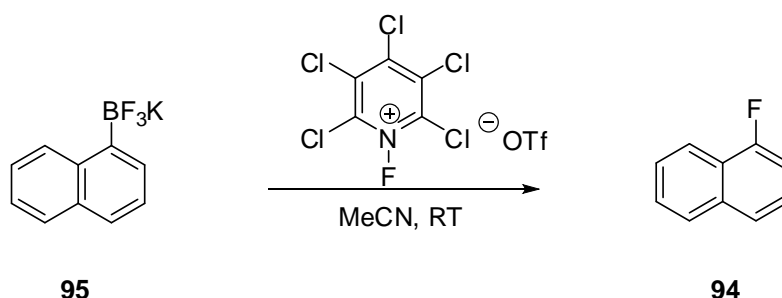


Scheme 56: Fluoro-deboronation of potassium trifluoro(naphthalene-1-yl)borate

The reaction was repeated with 2,6-lutidine, as an additive, to reduce the amount of difluorinated material obtained. Similar work by Ritter⁵¹ has shown that if an additive is used, this can reduce the di-fluorination of silanes. He found that, for electron-rich

systems, significant di-fluorination occurred and this could be reduced by the addition of 1 equivalent of 2,6-lutidine. It is thought that this may alter the basicity of the system or, alternatively, the pyridine of the 2,6-lutidine can react with the HF by-product which could react with the naphthalene. On addition of 1 equivalent of 2,6-lutidine to the reaction mixture, however, no decrease in the difluorinated material was observed. Other additives such as barium oxide, used by Ritter, also did not reduce the quantity of difluorinated material.

A comparative fluorination using 2,3,4,5,6-pentachloro-1-fluoropyridinium salt as the fluorinating agent (Scheme 57), using the same conditions, gave the desired product but with even more fluorinated side products forming. In contrast, fluorination with less powerful fluorinating agents such as the corresponding 1-fluoropyridinium salt and 4-cyano-1-fluoropyridinium gave no fluorinated product, even when the reaction mixture was heated to reflux and reaction times extended to 3 days.



Scheme 57: Fluoro-deboronation using the 2,3,4,5,6-pentachloro-1-fluoropyridinium salt

These results show that a powerful fluorinating agent, such as Selectfluor™ or 2,3,4,5,6-pentachloro-1-fluoropyridinium salt, is required for fluoro-deboronation to proceed although Selectfluor™ gave the best selectivity and conversion. These investigations also show that the potassium trifluoroborate salt is the more suitable boronic acid derivative and, although the trifluoroborate was shown to be the significantly more reactive than the boronic acid derivative, further fluorination reactions will be carried out using both the boronic acid and trifluoroborate to give a definitive, comparative study. The boronate esters will not be investigated further as they are not reactive or selective enough.

3.3.2.2 Fluoro-deboronation of Alkyl, Aryl and Biphenylboronic Acids

Table 10: Fluoro-deboronation of alkyl/arylboronic acids with SelectfluorTM

Y = BPin, B(OH)₂, BF₃K

Boronic Acid	Ar-F: Ar-H ¹	Yield/ %	Trifluoroborate	Ar-F: Ar-H ¹	Yield/ %
 96	1:1	10	 97	10:1	10 *
 98	3:2	51	 99	20:1	92 **

¹ Ar-F:Ar-H ratio measured by GC-MS, ² conversion measured by ¹H NMR Spectroscopy

* Combined Ar-H/Ar-F yield, ** isolated yield of Ar-F

3.3.2.2.1 Fluoro-deboronation of Potassium (4-*tert*-butylphenyl)trifluoroborate

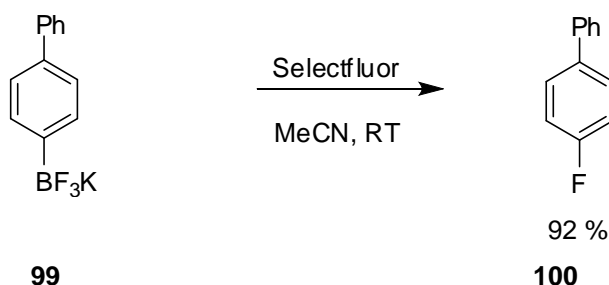
Lemaire *et al*⁶⁴ fluorinated potassium (4-*tert*-butylphenyl)trifluoroborate (**97**) and the equivalent boronic acid (**96**) (Table 10). Their research indicated that the boronic acid was the better substrate to use but both reactions gave over 50 % conversions. We repeated this reaction using the literature conditions (24 h stirring at RT) but this gave very slow conversion to the arylfluoride which could be due to poor solubility of the boronic acid in MeCN at room temperature.

The fluorination of **97** was carried out at room temperature for 5 days and this did not improve the conversion. The reaction was then repeated at reflux for 6 h to see if heating the reaction improved the rate of the reaction. On work-up, however, the crude material was identified as 100 % proto-deboronated product by GC-MS and there were

no significant signals in the ^{19}F NMR spectrum. The desired fluoro-aromatic product is a volatile liquid and so it is also possible that any arylfluoride product could have evaporated on work-up. Repeated reactions were carried out, and each time poor conversion and proto-deboronation occurred.

3.3.2.2 Fluoro-deboronation of Potassium Biphenyl-4-yltrifluoroborate

Conversely to the previous reaction, fluorination of potassium biphenyl-4-yltrifluoroborate (**99**) proceeded very well to the desired 4-fluorobiphenyl (**100**), with 92 % isolated yield being achieved.



Scheme 58: Fluoro-deboronation of potassium biphenyl-4-yltrifluoroborate

The reaction was also very selective, giving only negligible amounts of difluorinated material. After aqueous work-up and recrystallisation, however, these by-products and biphenyl could be removed to give **99**, as white crystals, in excellent yield. When the analogous fluorination reaction was carried out using the **98**, the reaction was less selective and considerably more biphenyl was afforded, as shown in Scheme 58.

3.3.2.3 Fluoro-deboronation of Alkoxy- and Aryloxyphenylboronic Acid Systems

Lemaire *et al*⁶⁴ also described the fluorination of several benzyloxyboronic acids. It was shown that these could be fluorinated very efficiently, with little side-products formed. A range of phenoxy-, methoxy- and ethoxyphenyl boronic acids and trifluoroborate salts will be fluorinated to examine the scope of this reaction.

Table 11: Fluoro-deboronation of alkyl- and aryloxyphenylboronic acids with SelectfluorTM

Y = BPin, B(OH)₂, BF₃K

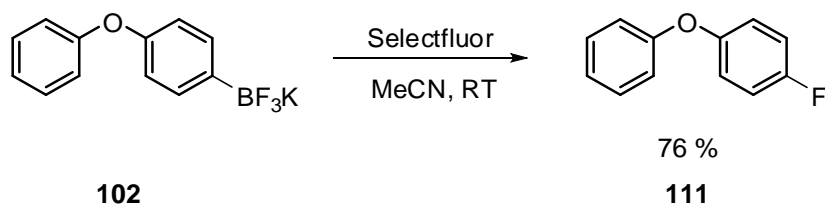
Boronic Acid	Ar-F: Ar-H ¹	Isolated Yield/ %	Trifluoroborate	Ar-F: Ar-H ¹	Isolated Yield/ %
 101	4:1	69	 102	20:1	76
 103	1:1	20	 104	9:1	72
 105	3:2	55	 106	9:1	71
 107	2:1	40	 108	4:1	75
 109	3:2	57	 110	4:1	56

¹ Ar-F:Ar-H ratio measured by GC-MS

We investigated a series of these processes and Table 11 shows the yield of the boronic acid/trifluoroborate to the desired fluoro-deboronation, Ar-F, product and the undesired proto-deboronated, Ar-H, product. The results show that proto-deboronation problem is reduced in electron rich systems when the trifluoroborate salt is used instead of the boronic acid. All these results will be discussed in more detail below.

3.3.2.3.1 Fluoro-deboronation of Potassium Trifluoro(4-phenoxyphenyl)borate

The reaction of potassium trifluoro(4-phenoxyphenyl)borate (**102**) with SelectfluorTM gave better yield than the equivalent boronic acid (**101**), with 76 % isolated yield being obtained (Scheme 59).

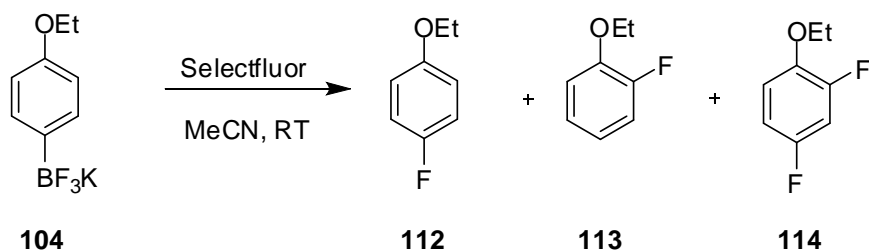


Scheme 59: Fluoro-deboronation of potassium trifluoro(4-phenoxyphenyl)borate

The 4-fluoro product (**108**) was identified by ^{19}F NMR spectroscopy with a multiplet at -120 ppm which is consistent with the literature value.⁷² After workup and purification of the crude product, the yield of the reaction was good. A small amount of difluorinated product remained (less than 3 %) but no proto-deboronated product could be identified. This is a good indication that phenoxyphenyl boronic acid derivatives are suitable substrates for this type of fluorination. Alkoxyphenylboronic acids will be investigated to see if these also exhibit the same kind of selectivity and reactivity.

3.3.2.3.2 Fluoro-deboronation of Potassium Trifluoro(4-ethoxyphenyl)borate

The fluoro-deboronation of 4-ethoxyphenylboronic acid (**103**), however, was very slow, with poor conversion from the boronic acid, even with 4 days stirring at RT and a high ratio of proto-deboronated product being identified. The fluoro-deboronation of the potassium trifluoroborate derivative (**104**), however, after 24 h stirring at room temperature was more successful. The ^{19}F NMR spectrum of the crude product indicated that the desired 1-ethoxy-4-fluorobenzene (**112**) had been afforded, as well as the 2-fluoro isomer and difluorinated products.



Scheme 60: Fluoro-deboronation of potassium trifluoro(4-ethoxyphenyl)borate

Figure 14 shows that, although the **112** was the major product at δ_{F} -124 ppm, there were also significant quantities (over 15 %) of difluorinated product (**114**) (δ_{F} -120 ppm and δ_{F} -132 ppm) and *ortho* mono-substituted product (**113**) (δ_{F} -135 ppm) present and

these were difficult to separate from the desired 4-fluoro derivative. Although this reaction produced low quantities of the proto-deboronated product, it was thought that the selectivity could be improved further.

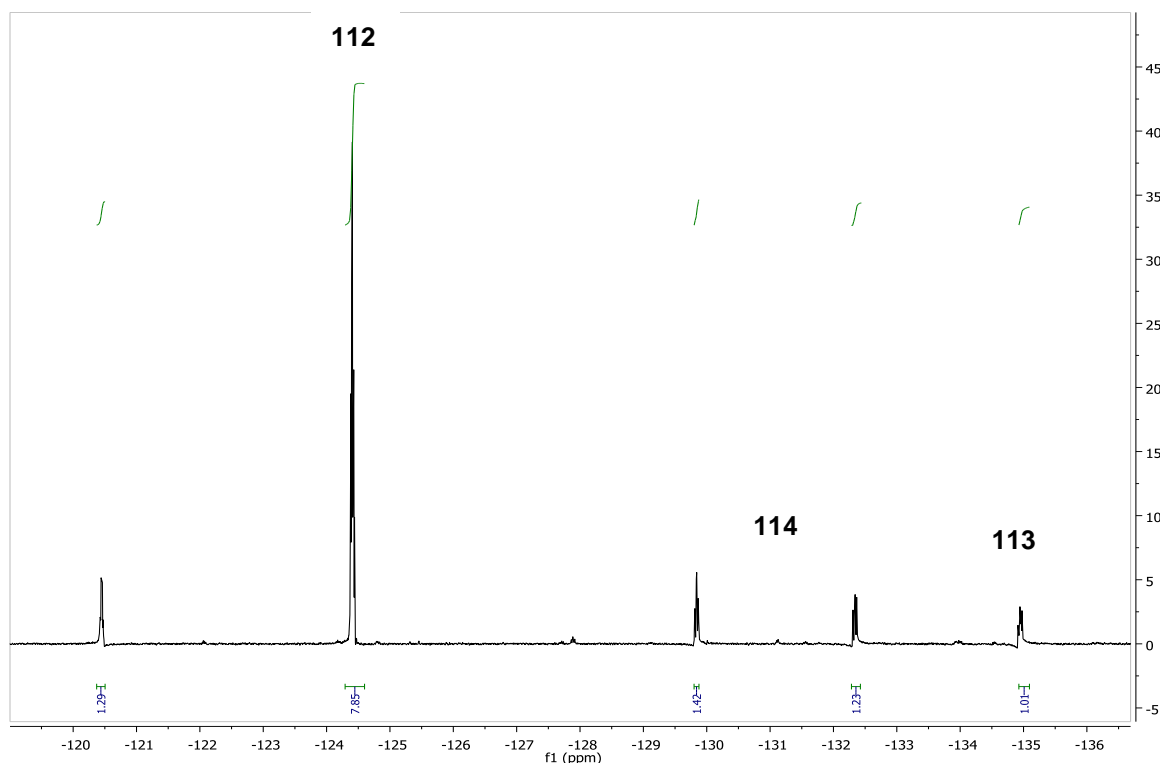
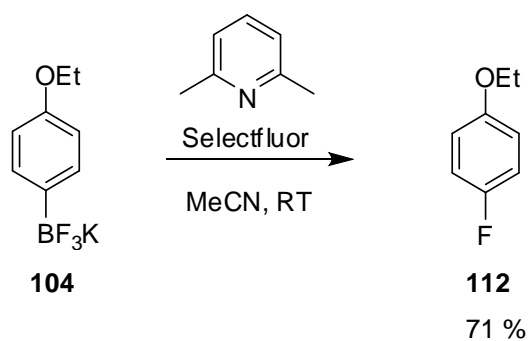


Figure 14: ^{19}F NMR spectrum from the fluoro-deboronation of potassium trifluoro(4-ethoxyphenyl)borate

The reaction was repeated with the same conditions but with 0.9 equivalents of SelectfluorTM to see if the SelectfluorTM was causing the di-fluorination to occur. The ^{19}F NMR spectrum of the crude product, however, showed the same ratio of products, with no improvement in the selectivity. An alternative approach was therefore sought. The reaction was repeated, with the same reaction conditions but with the addition of 1 equivalent of 2,6-lutidine (Scheme 61) and this improved the fluoro-deboronation reaction, with the ratio of difluorinated by-products reduced to less than 5 % (Figure 15).



Scheme 61: Fluoro-deboronation of potassium trifluoro(4-phenoxyphenyl)borate

Removal of 2,6-lutidine was facile by column chromatography and so the desired product, **112**, could be obtained in good yield. This result further indicates that the fluorination of electron-rich arylboronic acid systems is an efficient method for the synthesis of arylfluorides, with 2,6-lutidine being an effective additive to prevent di-fluorination.

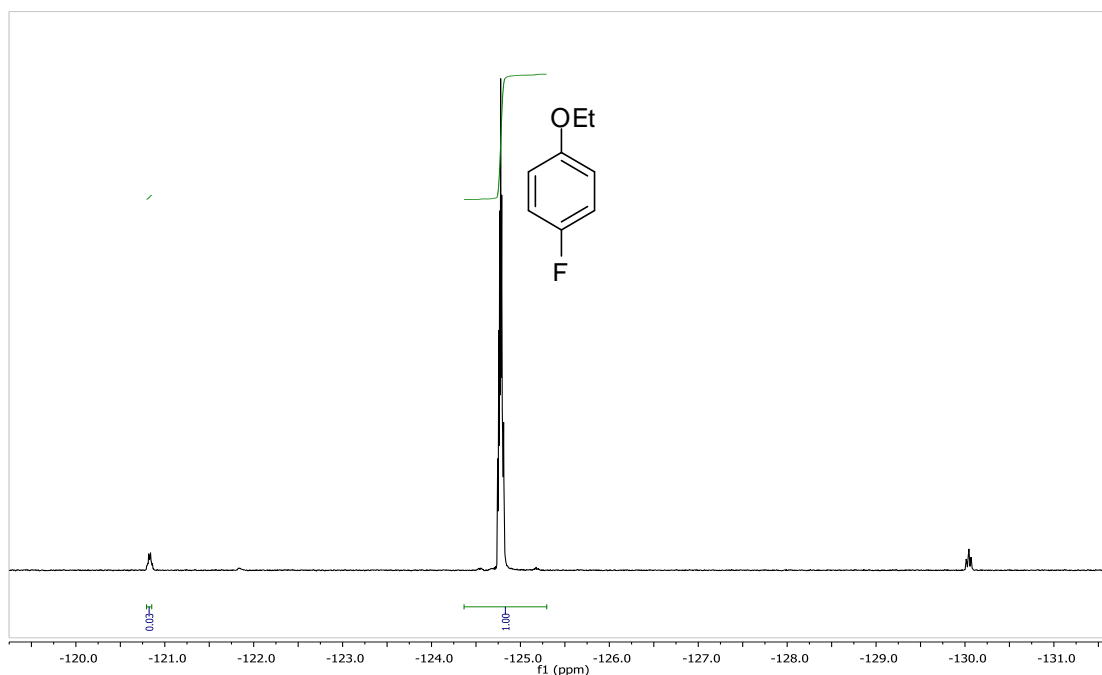
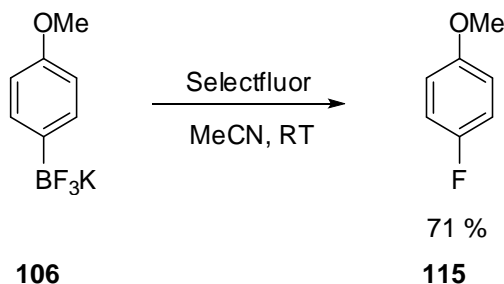


Figure 15: ^{19}F NMR spectrum from the fluorination of potassium trifluoro(4-ethoxyphenyl)borate with 1 equivalent of 2,6-lutidine

3.3.2.3.3 Fluoro-deboronation of Potassium Trifluoro(4-methoxyphenyl)borate

The fluoro-deboronation reaction of the 4-methoxy- derivative also proceeded very well when the trifluoroborate (**106**) was used instead of the boronic acid, with a 71 % isolated yield of 4-fluoromethoxybenzene (**115**) being gained (Scheme 62).

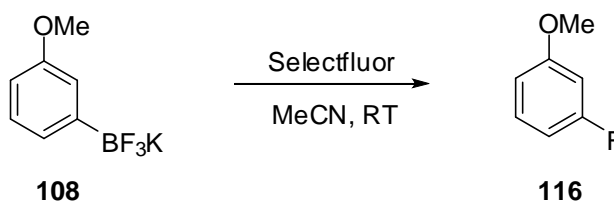


Scheme 62: Fluoro-deboronation of potassium trifluoro(4-methoxyphenyl)borate

Again, some difluorinated by-product was obtained (< 3 %) but only a small amount of the proto-deboronated product could be identified, as shown in Table 11. This reaction compares well with the fluorination of aryltriflate derivatives by Buchwald.⁵⁵ Buchwald showed that the *meta* isomer was preferred (70:30 *meta*: *para* ratio) when 4-methoxyphenyl trifluoromethanesulfonate was fluorinated under palladium catalysis.

3.3.2.3.4 Fluoro-deboronation of Potassium Trifluoro(3-methoxyphenyl)borate

Initial reactions with the potassium trifluoro(3-methoxyphenyl)borate (**108**) and 3-methoxyphenylboronic acid (**107**) with SelectfluorTM showed that this reaction was not selective (Scheme 63). In both cases, there were seven significant signals in the ¹⁹F NMR spectrum and the ¹H NMR spectrum showed that multiple products were present. A solid also precipitated from the reaction mixture which was removed by filtration and shown to be the starting boronic acid/trifluoroborate.



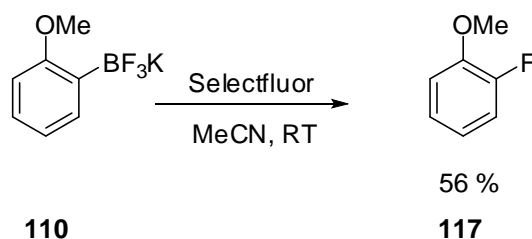
Scheme 63: Fluoro-deboronation of potassium trifluoro(3-methoxyphenyl)borate

This result is similar to those of Eaborn⁵⁹, who showed, with the bromination of arylsilanes, that the *meta*-isomer is highly activated towards bromination at the *para* and *ortho* position i.e. bromination at activated sites rather than bromo-deboronation at the *ipso* site occurs. The same reaction with the 2-substituted aryl was carried out to see if the 2-position also results in non-selective fluorination or if the 2-fluoroanisole can be afforded selectively and in good yield by fluoro-deboronation.

3.3.2.3.5 Fluoro-deboronation of Potassium Trifluoro(2-methoxyphenyl)borate

The 2-methoxy- derivative was also investigated as it was hoped that this would react similarly to the 4-isomer (Scheme 64). In the case of the boronic acid (**109**), the ¹⁹F NMR spectrum showed three signals at δ_F -124 ppm, δ_F -132 ppm and δ_F -136 ppm. The literature value³⁴ for **117** is δ_F -136.0 ppm.

In the case of the trifluoroborate (**110**), there was one main fluorine signal at δ_F -136.1 ppm as well as other much smaller signals but these contributed to less than 10 % of the NMR yield and **117** could be isolated in 56 % yield.



Scheme 64: Fluoro-deboronation of potassium trifluoro(2-methoxyphenyl)borate

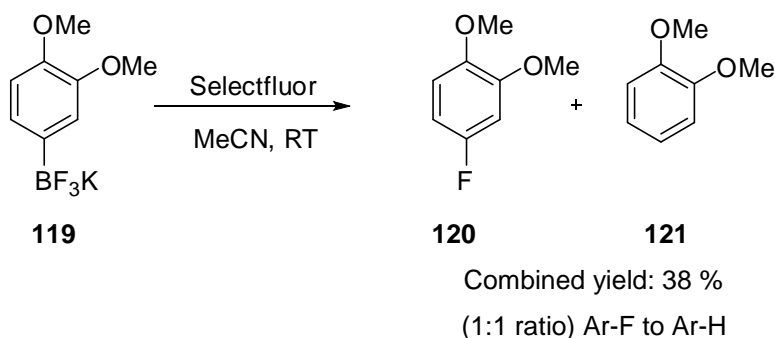
This shows that the fluorination of aryl trifluoroborates with SelectfluorTM is possible when there is an electron-rich substituent present, on the ring, in the *ortho* position. Since this is also possible for the *para*-substituted aryl trifluoroborate but not for the *meta*-substituted trifluoroborate, this indicates that the mechanism promotes the *ipso*-substituted fluorination in the *ortho* and *para* position only.

3.3.3 Fluoro-deboronation of Di-substituted Electron-rich Arylboronic Acids

Although the fluoro-deboronation of mono-substituted arylboronic acid derivatives gave some interesting results, fluorination of more complex electron-rich arylboronic acid derivatives were fluorinated to further investigate the scope of this reaction

3.3.3.1 Fluoro-deboronation of Potassium (3,4-dimethoxyphenyl)trifluoroborate

When 3,4-dimethoxyphenylboronic acid (**118**) and potassium (3,4-dimethoxyphenyl)trifluoroborate (**119**) were fluorinated with Selectfluor™ at RT (Scheme 65), a significant amount of tar was produced and very little fluorinated product could be identified from the ^{19}F NMR spectrum. Both reactions were repeated at 0 °C and this still produced significant quantities of tar and slowed the reaction to such an extent that more than 50 % boronic acid/trifluoroborate salt was present after 36 hours stirring.



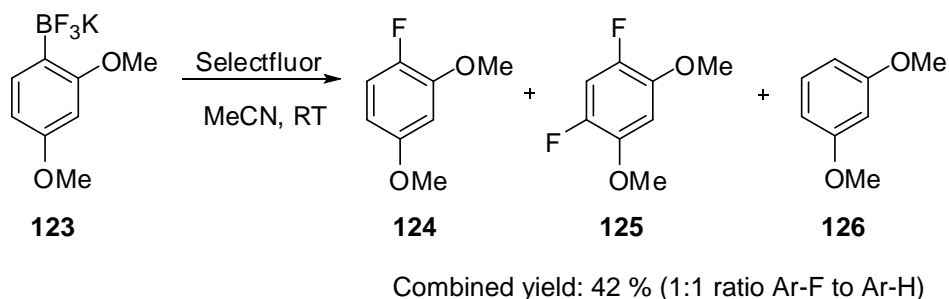
Scheme 65: Fluoro-deboronation of potassium (3,4-dimethoxyphenyl)trifluoroborate

Use of 2,3,4,5,6-pentachloro-1-fluoropyridinium triflate and 2,4-dichloro-1-fluoropyridinium triflate were investigated but these, again, resulted in mainly tar formation although some evidence of fluorinated products could be identified by ^{19}F NMR spectroscopy, but there was no selectivity and the yields were poor.

3.3.3.2 Fluoro-deboronation of Potassium (2,4-dimethoxyphenyl)trifluoroborate

The fluoro-deboronation of 2,4-dimethoxyphenylboronic acid derivatives was assessed but was not selective and the ^{19}F NMR spectrum showed that both the mono- (δ_{F} -141

ppm) and di-fluorinated (δ_F -146 ppm) products, in a 2:1 ratio (mono:di), as well as the proto-deboronated product were obtained, as shown in Scheme 66. This was the case with both the arylboronic acid (**122**) and potassium trifluoroborate salt (**123**).

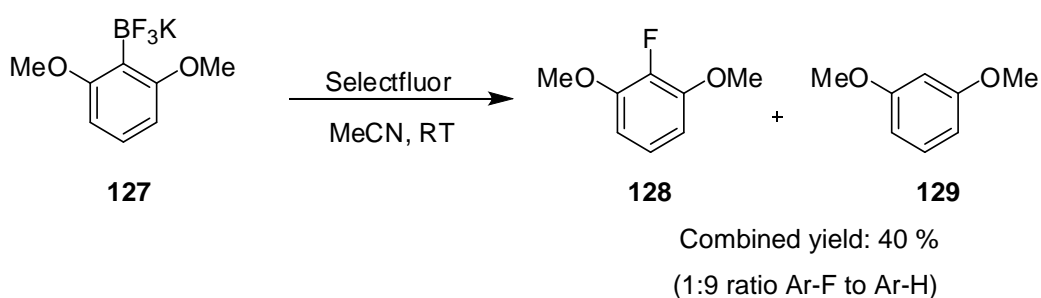


Scheme 66: Fluoro-deboronation of potassium(2,4-dimethoxyphenyl)trifluoroborate

This reaction was no improvement on the direct fluorination of di-substituted aromatics shown in Chapter 2, with no pure products isolated.

3.3.3.3 Fluoro-deboronation of Potassium (2,6-dimethoxyphenyl)trifluoroborate

Fluorination of potassium (2,6-dimethoxyphenyl)trifluoroborate (**127**) also gave poor selectivity and yield, on fluorination with SelectfluorTM (Scheme 67).



Scheme 67: Fluoro-deboronation of potassium (2,6-dimethoxyphenyl)trifluoroborate

The selectivity in this reaction was very poor, with many signals in the ^{19}F NMR spectrum as well as a significant ratio of proto-deboronated product (**129**) (Figure 16). The desired product (**128**) has a ^{19}F NMR shift of δ_F -159.5 ppm³² and it can be seen from the spectrum below that this was not obtained as a single product.

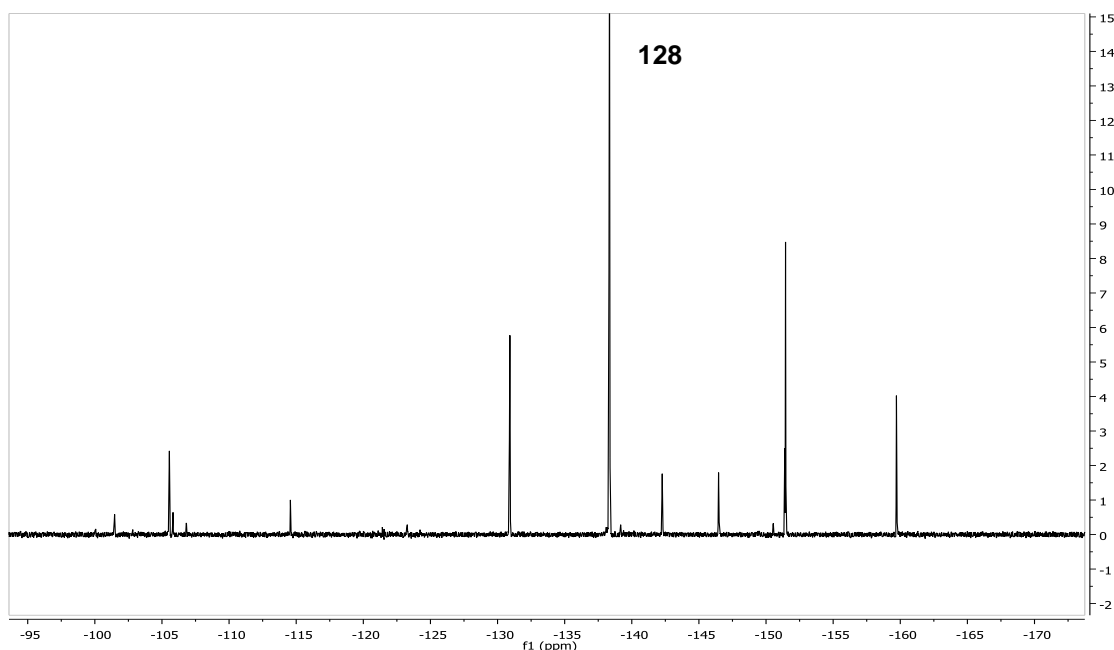


Figure 16: ^{19}F NMR spectrum from the fluoro-deboronation of potassium (2,6-dimethoxyphenyl)trifluoroborate

3.3.4 Fluoro-deboronation Fluorination of Arylboronic Acid Systems Containing an Electron-rich and Electron-poor Substituent

The fluorination of di-substituted electron-rich arylboronic acid systems gave poor conversion and little selectivity, with fluorination at many sites. Since these systems are highly activated, it was proposed that having an electron-withdrawing group on the ring may reduce the activity of the system, thereby allowing a more selective reaction to occur. Consequently, a range of these systems were studied, as shown in Table 12.

Table 12: Fluoro-deboronation of boronic acid systems containing an electron-rich and electron-poor substituent

Y = B(OH)₂, BF₃K
 EDG = OMe
 EWG = CHO, Cl

Boronic Acid	Ar-F: Ar-H ¹	Yield/ %	Trifluoroborate	Ar-F: Ar-H ¹	Yield/ %
<p>130</p>	1:1	30	<p>131</p>	7:3	62 **
<p>132</p>	1:15	10	<p>133</p>	1:1	39 *
<p>134</p>	1:1	42	<p>135</p>	1:1	44 *
<p>136</p>	2:3	40	<p>137</p>	1:1	43 *

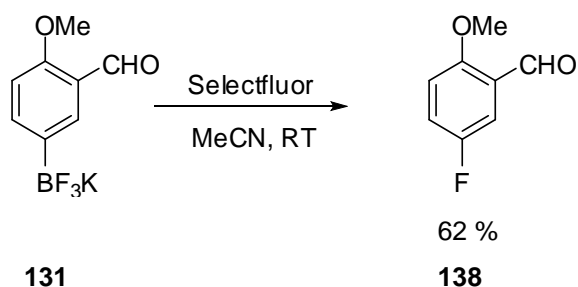
¹ Ar-F:Ar-H ratio measured by GC-MS

* Combined Ar-H/Ar-F yield, ** isolated yield of Ar-F

3.3.4.1 Fluoro-deboronation of Potassium Trifluoro(3-formyl-4-methoxyphenyl)borate

The fluorination reaction of **131** proceeded well and gave only one signal in the ¹⁹F NMR spectrum in the correct position (-123 ppm) for the desired product, **138** (Scheme 68). GC-MS indicated, however, a significant amount of the proto-deboronated product was present (30 %). The reaction with the boronic acid analogue (**130**), however, gave significantly more proto-deboronated product, as shown in Table 12. It was thought that

the instability of the strongly electron-withdrawing substituent on the aryltrifluoroborate and arylboronic acid increases its tendency to undergo proto-deboronation.



Scheme 68: Fluoro-deboronation of potassium trifluoro(3-formyl-4-methoxyphenyl)borate

2,3,4,5,6-Pentachloro-1-fluoropyridinium triflate was used as an alternative fluorinating agent and this gave two main fluorinated products and other fluorinated by-products as well as the proto-deboronated product. Since this *N*-fluoropyridinium salt was too reactive, the less reactive 2,6-dichloro-1-fluoropyridinium triflate was used but the amount of fluorinated material was not improved and further by-products were afforded, as can be seen in Table 13.

Table 13: Fluoro-deboronation of potassium trifluoro(3-formyl-4-methoxyphenyl)borate

N-F reagent	Ar-F: Ar-H ¹	Yield/ %
Selectfluor™	7:3	62 **
2,6-dichloro-1-fluoropyridinium triflate	3:2	45 *
2,3,4,5,6-pentachloro-1-fluoropyridinium triflate	1:9	39 *

¹ Ar-F:Ar-H ratio measured by GC-MS

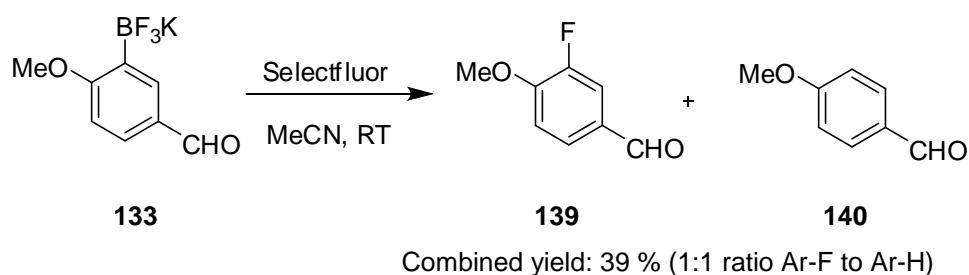
* Combined Ar-H/Ar-F yield, ** isolated yield of Ar-F

The reaction was also repeated with the addition of molecular sieves to see if this could reduce the quantity of proto-deboronated product afforded. Unfortunately, no reduction in the proto-deboronation could be achieved and so since the fluorination with Selectfluor™ gave the best yield this was repeated on a larger scale and **138** isolated in 62 % yield. This is an excellent result as it shows that the fluorination at the *ipso* position of trifluoroborate salts is possible, even when an electron-withdrawing substituent is present.

3.3.4.2 Fluoro-deboronation of Potassium 5-Formyl-2-methoxyphenyl trifluoroborate

The fluorination of **131** proceeded well and so an alternative isomer, 5-formyl-2-methoxyphenylboronic acid (**132**) and potassium trifluoroborate salt (**133**), were investigated.

The fluorination of **132**, however, resulted in very little fluorination reaction, with starting material recovered. The fluorination of **133** with Selectfluor™ was, however, more successful and a 39 % yield obtained, with a multiplet at δ_F -134 ppm in the ^{19}F NMR spectrum. Unfortunately, it was found that the product also contained the unwanted proto-deboronated product (**140**) with a 1:1 ratio of Ar-F and Ar-H (Scheme 69). Alternatively, with *N*-fluoropentachloropyridinium triflate as the electrophilic fluorine source, mainly proto-deboronated product was obtained.



Scheme 69: Fluoro-deboronation of potassium 5-formyl-2-methoxyphenyltrifluoroborate

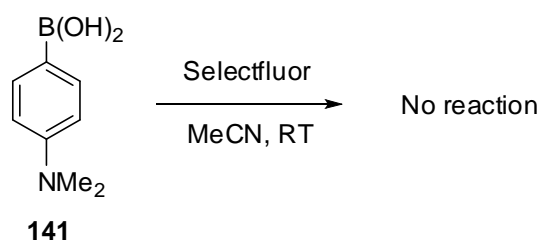
The product could not be separated by chromatography due to the similarity of the R_f values of the fluoro- and proto-deboronated products. Repeated recrystallisations were also unsuccessful in separating out the arylfluoride product.

Although the arylfluoride could not be isolated, the results indicate that the fluorination reaction is successful, but the problem is the competing proto-deboronation reaction. If a method could be found to prevent proto-deboronation then this could be an excellent method for the synthesis of arylfluorides containing both electron-rich and electron-poor substituents.

3.3.5 Fluoro-deboronation of Aminophenylboronic Acid Systems

3.3.5.1 Fluoro-deboronation of 4-(Dimethylamino)phenylboronic acid

It has been shown that boronic acids/trifluoroborates can be fluorinated when they contain an electron-donating group such as methoxy-, ethoxy- and phenoxy in the *ortho* or *para* position. Similar arylboronic acids with alternative, electron-rich, functional groups were also investigated. However, the reaction of 4-(dimethylamino)phenylboronic acid (**141**) and Selectfluor™ afforded a black liquid with no fluorine signals in the ^{19}F NMR spectrum.



Scheme 70: Fluoro-deboronation of 4-(dimethylamino)phenylboronic acid

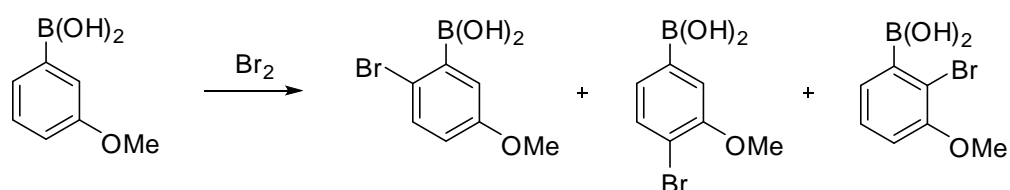
It is likely that the dimethylamino- group was oxidised as the nitrogen is susceptible to oxidation. Attempts were made to make the trifluoroborate salt, but these also failed. Since amino- substituted phenylboronic acids are susceptible to oxidation, no more work was carried out using these substrates.

3.3.6 Mechanism of Fluoro-Deboronation of Arylboronic Acids

For the analogous bromo-deboronation of boronic acids, Kuivila^{73–76} suggested that if cleavage of the carbon-boron bond were important in the rate-determining step it would be facilitated by electron-withdrawing groups, particularly when in the *ortho* or *para*

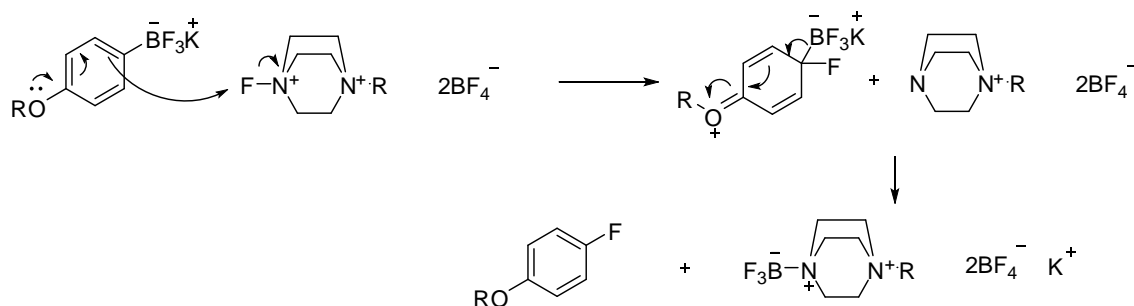
positions. He proposed that one of the reacting species in the rate-determining step is a quadri-covalent boron derivative and it would be expected that electron-donating groups would decrease the concentration of such an intermediate and thus the effect on the brominolysis rate would be the reverse of that actually observed. Therefore, this factor must be relatively unimportant in determining the relative rates.

Similarly to the fluoro-deboronation of 3-methoxyphenyl boronic acid derivatives, Kuivila also found that bromination of *meta*-substituted boronic acids underwent a different reaction to that expected.⁷³ Instead of displacement of the boronic acid, direct bromination of the ring occurred, as shown in Scheme 71. Functional groups with high capacity for conjugative electron release can activate the *ortho* and *para* positions towards electrophilic attack so that the protons in these positions are replaced preferentially. This conclusion also agrees the results of bromo-desilylation found by Eaborn.^{59, 77}



Scheme 71: Bromo-deboronation of *meta*- substituted boronic acids

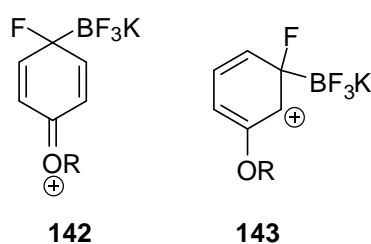
The exact mechanism of the *ipso* fluoro-deboronation reactions discussed above is unknown, although some understanding of the mechanism has been achieved. It is thought that electrophilic attack occurs to give the stable arenium intermediate, which then re-aromatises with the boronate as the leaving group (Scheme 72). The substituents on the aromatic ring, however, have a large effect on the outcome of the reactions.



Scheme 72: Proposed mechanism of fluoro-deboronation

The competing proto-deboronation reaction may result from a proton attacking the boronic acid, in place of the electrophilic F^+ salt. It is possible that the proton source is from trace water in the acetonitrile, although use of dry acetonitrile did not reduce the ratio of proto-deboronated products. It may also form from DABCO, the by-product remaining from the reacted Selectfluor™ although addition of a base to the reactions resulted in no reaction occurring.

Reactions of trifluoroborate salts containing an electron-donating group in the 4-position have been shown to be more reactive than their corresponding 2-isomer. This can be explained by the effect of the charge density at the carbon atom bearing the borate group and the stability of the arenium intermediate formed by the *ipso* attack at this carbon atom. It is known that the stability of the *para* arenium ion intermediate is more stable than the *ortho* equivalent, as *para* substituents have a greater stabilising effect on the adjacent carbon.⁷⁸ This means that the intermediate **142** would be expected to form fastest due to the higher electron density on the carbon atom bearing the boronate group available for electrophilic attack and thus lead to a more stable arenium ion intermediate after the attack of the electrophile.⁷⁹ This explains why the fluoro-deboronation of electron-deficient arylboronic acids failed to give the desired fluoroaromatics because the electron-withdrawing groups destabilise the carbocation intermediate. This also explains why the *meta*-substituted boronic acid derivatives (**143**) do not react in the same way, as the carbo-cation cannot be stabilised by the substituent.



It has also been shown, in the case of the 2-methoxyphenylboronic acid derivatives, that steric effects may have an outcome on the reaction rate. In the case of the potassium trifluoro(2-methoxyphenyl)borate (**110**), the conversion and yield of the reaction were both lower than in the case of the 4-isomer (**106**), which may be due to steric stress on the *ipso* carbon by the 2-methoxy- substituent.

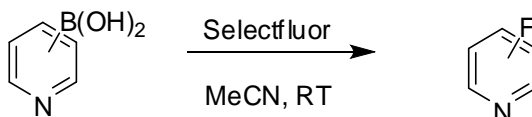
3.3.7 Fluoro-deboronation of Heterocyclic Boronic acid Systems

It has been shown in previous chapters, that it is difficult to selectively fluorinate heterocyclic systems. Fluoride ion reagents such as KF, HF, Et₃N.3HF can be used for the displacement of suitable leaving groups such as halogens or diazo substituents but the synthesis of the appropriate functional heterocyclic precursor can be difficult and fluorination generally requires activated heterocyclic starting materials. There are also examples of selective direct fluorination reactions of heterocyclic systems such as pyridine⁸⁰, quinoline⁸¹ and coumarin⁸² systems but the fluorination only occurs in these on the benzenoid ring. Conversely, the fluorination of pyrroles by electrophilic fluorinating agents gives polymeric material.

It would be interesting to see if the electrophilic fluorination of heterocyclic boronic acids could afford fluoro-heterocyclic systems since these are very important in the pharmaceutical industry. However, 2-heterocyclic, vinyl, and cyclopropyl boronic acids are known to decompose in air via proto-deboronation, oxidation, and/or polymerization. These processes are also thought to be accelerated in the presence of heat and base causing the *in situ* decomposition of unstable boronic acids to compete with the desired reaction pathway.⁸³

3.3.7.1 Fluoro-deboronation of Pyridyl Boronic Acids

The fluorination of pyridin-4-ylboronic acid, pyridin-3-ylboronic acid and pyridin-2-ylboronic acid was carried out using the general fluoro-deboronation procedure (Scheme 73). In all cases no fluorinated product could be seen in the ¹⁹F NMR spectrum. The reactions were also repeated at reflux for 48 h but again, no fluorinated product could be identified by ¹⁹F NMR spectroscopy and GC-MS.



Scheme 73: Fluoro-deboronation of pyridyl boronic acids using SelectfluorTM

Pyridyl boronic acids with electron-donating substituents in the 2/6 position and the boronic acid at the 3/5 position will, therefore, be explored to see if this promotes the fluorination reaction.

3.3.7.1.1 Fluoro-deboronation of Potassium Trifluoro(6-methoxypyridin-3-yl)borate

The synthesis of 5-fluoro-2-methoxypyridine (**143**) is usually achieved by diazotisation⁸⁴ and there are no methods for the selective fluorination of this substrate. It was thought that the fluorination may proceed because this substrate could be seen as an analogue to the substrates with arylboronic acids containing one electron-donating and one electron-withdrawing substituent (Figure 17).

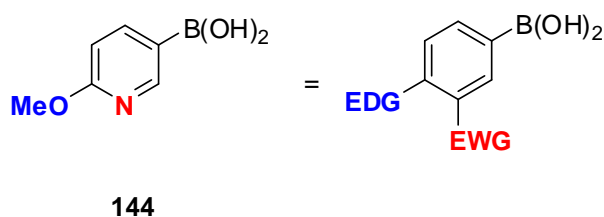


Figure 17: Fluoro-deboronation of pyridine boronic acids containing an electron-rich substituent

Although proto-deboronation of boronic acids containing one electron-donating and one electron-withdrawing substituent has been shown to be a problem, it would be interesting to see if this fluorination could proceed at all.

However, the reaction of 6-methoxypyridin-3-ylboronic acid (**144**) with Selectfluor™ was very slow and after 7 days stirring, only 10 % conversion to the fluoropyridine (**146**) had occurred, which was likely due to the very poor solubility of the boronic acid in acetonitrile. Potassium trifluoro(6-methoxypyridin-3-yl)borate (**145**) was therefore synthesised and fluorinated to see if this was a more reactive substrate as the salt was soluble in MeCN at RT (Scheme 74).

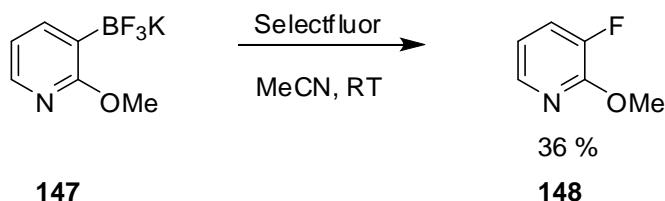


Scheme 74: Fluoro-deboronation of potassium trifluoro(6-methoxypyridin-3-yl)borate

The fluorination of **145** gave 40 % conversion (by ^1H NMR spectroscopy) to the fluorinated product, **146**, after 3 days stirring, with no proto-deboronated product seen in the NMR spectra or GC-MS. Unfortunately, after 7 days stirring at room temperature, the conversion had not improved and so **146** was isolated by column chromatography in 34 % isolated yield after a brine wash to remove any excess **145**. The reaction was repeated with two equivalents of SelectfluorTM but this did not improve the conversion and similarly, heating the reaction to 80 °C did not improve the yield of the arylfluoride. This is an interesting result as there are, currently, no reported examples of heterocyclic trifluoroborate salts being fluorinated, without the use of a metal catalyst.

3.3.7.1.2 Fluoro-deboronation of Potassium Trifluoro(2-methoxypyridin-3-yl)borate

Since the fluoro-deboronation of **146** was successful, the fluorination of the 2-isomer, potassium trifluoro(2-methoxypyridin-3-yl)borate (**147**), was investigated and gave a similar result (Scheme 75). 3-Fluoro-2-methoxypyridine (**148**) was isolated in 36 % yield.

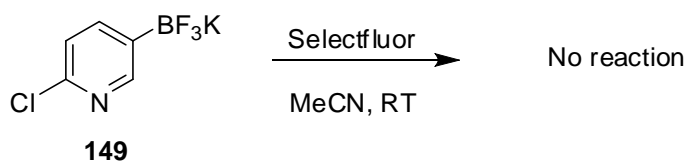


Scheme 75: Fluoro-deboronation of potassium trifluoro(2-methoxypyridin-3-yl)borate

A brine wash was used to remove excess **147** and after the wash, ^{19}F NMR spectroscopy and GC-MS confirmed that **148** had been obtained and showed a multiplet at δ_{F} -140.2 ppm, with 4 % of a difluorinated material also present at δ_{F} -135.8 ppm.

3.3.7.1.3 Fluoro-deboronation of Potassium Trifluoro(6-chloropyridin-3-yl)borate

The fluorination of pyridyl trifluoroborate salts is possible, as described above, when an electron-donating substituent (OMe) is attached to the 2- or 6-position and when the trifluoroborate is located at the 3-position. It was hoped that the reaction of pyridyl trifluoroborate salts containing an electron-withdrawing group at the 2 or 6 position would afford the fluorinated pyridine.

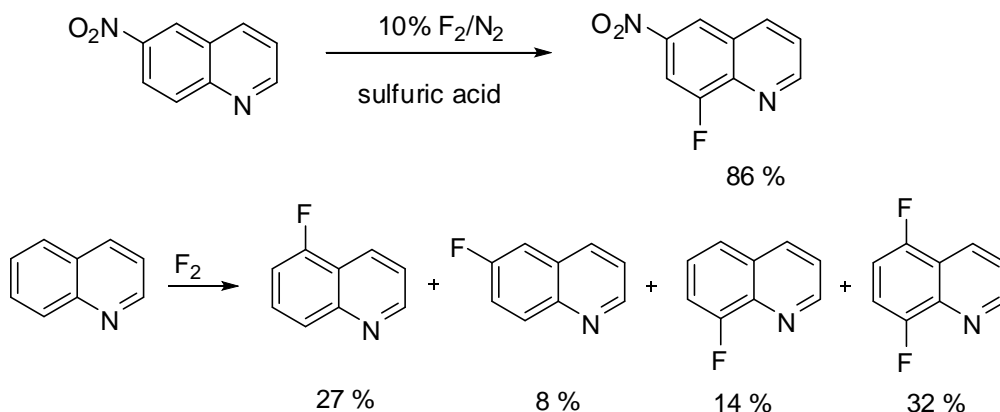


Scheme 76: Fluoro-deboronation of 2-methoxypyridin-3-ylboronic acid

Unfortunately, several reactions with SelectfluorTM and potassium trifluoro(6-chloropyridin-3-yl)borate (**149**), in various conditions, gave only a complex mixture of products, with no significant fluorine signals in ¹⁹F NMR spectrum (Scheme 76). On heating the reaction, no improvement in conversion to the arylfluoride was observed.

3.3.7.2 Fluoro-deboronation of Quinoline Boronic Acids

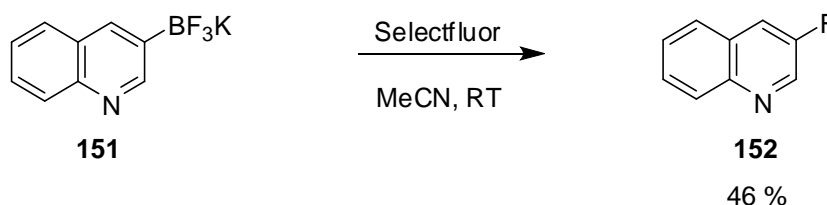
As an important class of alkaloids, quinoline compounds are of pharmaceutical interest due to their wide range of biological activities.⁸⁵ Direct fluorination of quinolines is possible but fluorination only occurs on the benzenoid ring. The fluorination of quinoline itself affords a mixture of fluorinated products (Scheme 77).



Scheme 77: Direct fluorination of quinolines

3.3.7.2.1 Fluoro-deboronation of Potassium Trifluoro(quinolin-3-yl)borate

Quinolin-3-ylboronic acid (**150**) was very poorly soluble in acetonitrile and so fluorination of the potassium trifluoro(quinolin-3-yl)borate (**151**) was investigated (Scheme 78).



Scheme 78: Fluoro-deboronation of potassium trifluoro(quinolin-3-yl)borate

After 4 days stirring at RT, the reaction was stopped and aqueous work-up carried out. ^{19}F NMR spectroscopy showed that a fluorinated product had been formed, showing a multiplet at δ_{F} -128.7 ppm. The ^1H NMR spectrum also showed a significant change in the signals in the aromatic region. Both mass and NMR spectroscopy indicated that no proto-deboronated product was present, although, the **151** was not fully converted, with only 50 % conversion gained. **151** could be easily separated from **152** by a brine wash. Unfortunately, on repeating the reaction and stirring at RT for 10 days, no increase in the conversion was observed. **152** was isolated pure in 46 % yield.

The fluorination of electron-rich pyridines and quinoline boronic acid derivatives show that the *ipso* fluorination of boronic acids is a viable method for the synthesis of fluoro-heterocycles.

3.3.7.3 Fluoro-deboronation of Indole Boronic Acids

3.3.7.3.1 Fluoro-deboronation of Potassium (1-(tert-butoxycarbonyl)-1H-indol-2-yl)trifluoroborate

As shown in Chapter 1, the *ipso* fluorination of heterocyclic stannanes, containing a protecting group at the ring nitrogen, using SelectfluorTM, is possible. It was found that proto-destannylation and di-fluorination occurs as well as the desired fluorination.⁴⁹ It

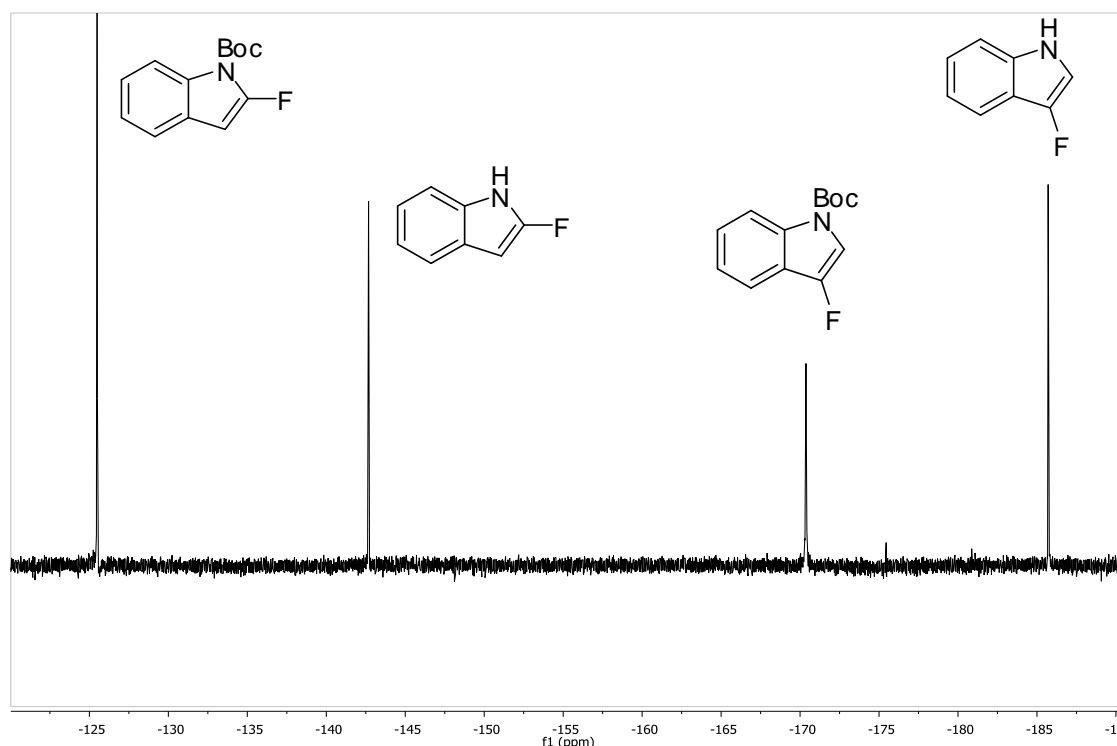


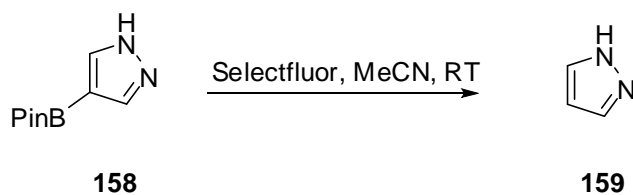
Figure 18: ^{19}F NMR spectrum from the reaction of potassium (1-(tert-butoxycarbonyl)-1H-indol-2-yl)trifluoroborate and SelectfluorTM

3.3.7.4 Fluoro-deboronation of Pyrazole Boronic Acids

3.3.7.4.1 Fluoro-deboronation of Potassium Trifluoro(1H-pyrazol-4-yl)borate

It was hoped that the fluorination using boronic acids to direct the fluorination to the *ipso* site would result in selective fluorination at the 4-position of pyrazole to give 4-fluoro-1H-pyrazole.

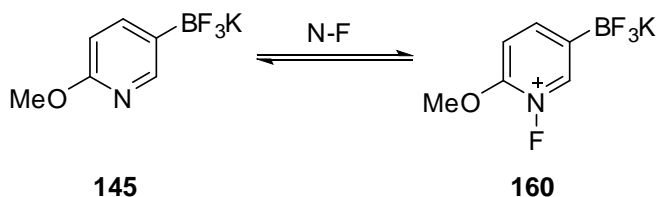
1H-Pyrazol-4-ylboronic acid is known to be unstable and so the equivalent pinacol ester (**158**) was used. Again, attempts to synthesise the more stable and reactive trifluoroborate salt was carried out. Instead of the desired fluorination reaction however, proto-deboronation occurred, to give the corresponding 1H-pyrazole (**159**). **158** was therefore fluorinated, using SelectfluorTM, but again, this gave 95 % yield of **159** (Scheme 80). The difficulty in this reaction is the instability of the pyrazole boronic acid species.



Scheme 80: Reactions on 1H-Pyrazol-4-ylboronic acid pinacol ester

3.3.7.5 Mechanism of Fluoro-Deboronation of Heterocyclic Boronic Acids

Little is known about the fluoro-deboronation of heterocyclic boronic acids. It has been observed that the conversion of the reaction is poor, with a significant quantity of starting material remaining in all reactions. This conversion could not be improved on addition of further equivalents of Selectfluor™ or heating. It was proposed that fluorination of the pyridine nitrogen may be occurring simultaneously to the fluoro-deboronation reaction causing the equilibrium between **145** and **160**, shown in Scheme 81.

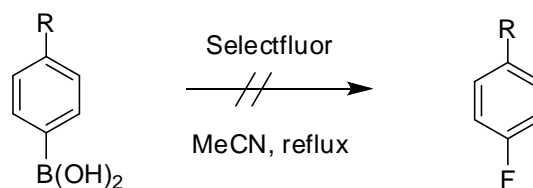


Scheme 81: Fluoro-deboronation of N-heterocyclic boronic acid derivatives

It is thought that the N-fluorinated product is hydrolysed back to the starting material on aqueous work-up. Attempts were made to observe this N-fluorinated species, by ^{19}F NMR spectroscopy, but no signals could be detected in the expected region of the spectrum.

3.3.8 Fluoro-deboronation of Electron-deficient Arylboronic Acid Systems

The fluorinations of electron-deficient aromatic systems, shown in Scheme 82, were carried out at room temperature, reflux and with microwave heating at 90 °C for up to 1 hour, with both Selectfluor™ (Scheme 82) and various N-fluoropyridinium salts as the electrophilic fluorinating agent.



R = NO₂, CN, CO₂H, CO₂Me

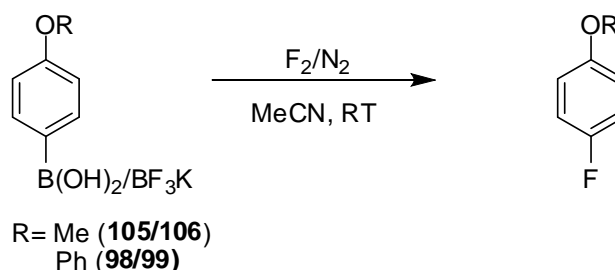
Scheme 82: Fluoro-deborylation of electron-deficient systems

In every case, only boronic acid could be recovered, with no fluorinated or proto-deboration products were formed, as shown by the mass spectroscopy and NMR analysis of crude reaction mixtures.

3.3.9 Reactions of Arylboronic Acids with Elemental Fluorine

It has been shown that electrophilic fluorination of boronic acids and trifluoroborate salts is possible when Selectfluor™, and to some extent when *N*-fluoropentachloropyridinium triflate, are employed as the fluorinating agents and so it is therefore possible that the fluorination may proceed when elemental fluorine (as 10 % F₂/N₂) is used as the electrophilic fluorinating agent. Various substrates were investigated, including systems with electron-donating groups that were successfully fluorinated with Selectfluor™, and systems with electron-withdrawing groups that could not be fluorinated using electrophilic N-F salts.

3.3.9.1 Fluoro-deboration of Phenylboronic Acid Systems bearing Electron-donating Substituents with Elemental Fluorine



Scheme 83: Fluoro-deboration of electron-rich phenyl boronic acids with fluorine

The fluorination of 4-methoxyphenylboronic acid (**105**) and the corresponding potassium trifluoroborate derivative (**106**) with elemental fluorine in acetonitrile, using the batch process, gave a complex mixture of products (Figure 83).

The complex mixture is likely to be due to rapid proto-deboronation, which gives anisole. The consequent fluorination of anisole is known to give many fluorinated products (Figure 19), including mono-fluorinated and di-fluorinated isomers. The proto-deboronation occurs quickly when elemental fluorine, which may be due to F₂ containing trace amounts of HF. HF is also a by-product of the fluorination reaction with anisole.

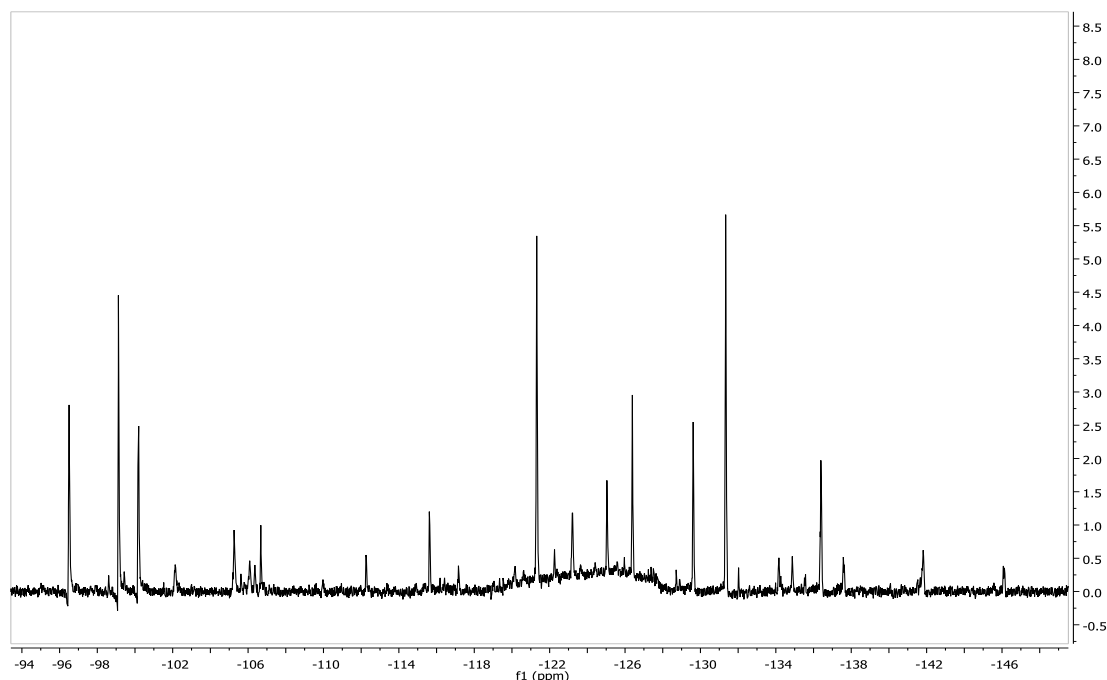


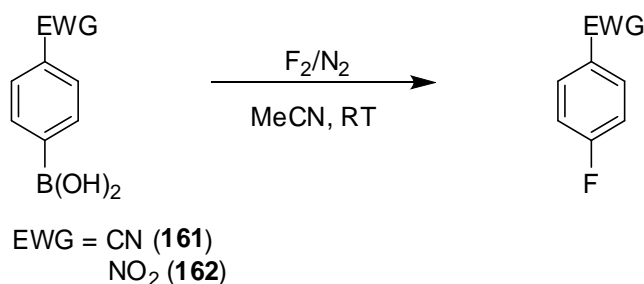
Figure 19: *¹⁹F NMR spectrum from the fluoro-deboronation of 4-methoxyphenylboronic acid (**98**) using elemental fluorine*

The reaction was also repeated with the phenoxyphenylboronic acid derivatives (**101** and **102**) to see if this was more stable with respect to proto-deboronation and, again, many fluorinated products were observed in the ¹⁹F NMR spectrum and further purification was not carried out.

3.3.9.2 Fluoro-deboronation of Phenylboronic Acid Systems bearing Electron-withdrawing Substituents with Elemental Fluorine

The fluorination of the activated boronic acid systems with elemental fluorine gave a complex mixture of products which could not be separated due to rapid proto-deboronation so deactivated boronic acid systems were investigated.

As described above, the fluorination of 4-cyanophenylboronic acid (**161**) with Selectfluor™ at reflux and RT did not result in a reaction occurring and it was hoped that using a more powerful fluorinating agent may promote the fluoro-deboronation reaction (Scheme 84).



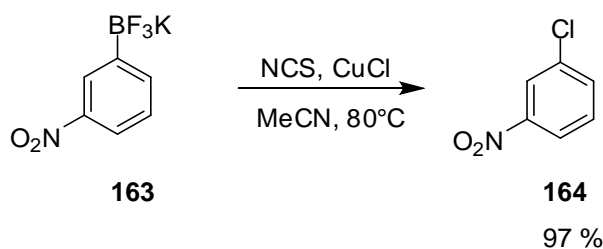
Scheme 84: Fluoro-deboronation of 4-cyanophenylboronic acid using elemental fluorine

As with other electrophilic fluorinating agents, there was no reaction with elemental fluorine, and only starting material remained. The same result occurred when other electron-deficient boronic acids were fluorinated with elemental fluorine (Scheme 84). This indicates that highly deactivated boronic acid substrates cannot be fluorinated using the present conditions.

3.3.10 Reactions of Arylboronic acids with Selectfluor™ and Copper Salts

As mentioned previously, research has been carried out by Hynes *et al* which shows that halogenation of boronic acid systems can be aided by the addition of a copper catalyst, particularly in the case of electron-deficient arylboronic acids (Scheme 85).⁸⁷ Hynes found that boronic acids and trifluoroborate salts gave the best conversions compared with only ~20 % conversion with pinacol esters. Hynes was able to show that the

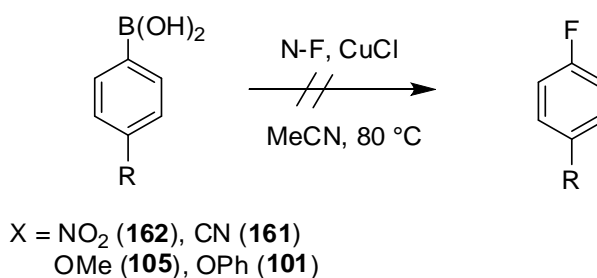
chlorination and bromination of arylboronic acids with a wide range of functional groups including, nitrile, aldehyde, acid, amide and ester, was possible.



Scheme 85: Chloro-deboronation of potassium 3-nitrotrifluoroborate

As this worked well with electrophilic brominating and chlorinating agents, it was thought that fluorine could be added to boronic acids using electrophilic fluorinating agents, such as Selectfluor™. The same procedure was used with CuCl, CuCl₂ and CuF₂ investigated as possible catalysts.

Initially, the reactions were carried out using Selectfluor™ and CuCl, at both 10 % and 100 % catalyst loading, as described by Hynes. The reaction was repeated with a variety of functional groups present on the arylboronic acid (Scheme 86). In all cases the reaction mixture turned dark brown and no signals could be seen in the ¹⁹F NMR spectrum, after aqueous work-up. The reactions were repeated with CuCl₂ and CuF₂, as the catalyst, and again no fluorinated products could be identified.

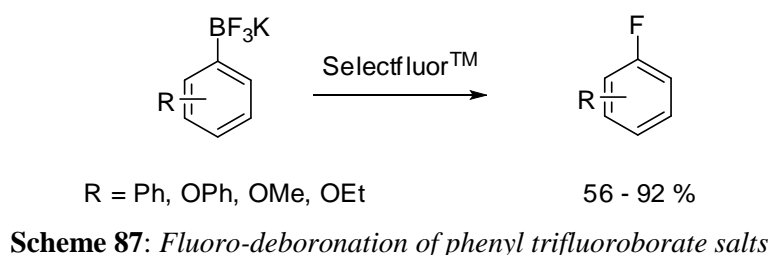


Scheme 86: Fluoro-deboronation of boronic acids with CuCl and Selectfluor™

Other electrophilic fluorinating agents, such as a range of *N*-fluoropyridinium salts were also investigated to see if these promote the catalysed fluorination reaction but again no reaction occurred.

3.4 Conclusions

The fluoro-deboronation of 4-phenyl- (**99**), 4-phenoxy- (**101**), 4-ethoxy- (**104**), 4-methoxy- (**106**) phenyltrifluoroborate systems gave the desired arylfluoride in good isolated yield, with very little difluorinated product being afforded (Scheme 87). Initial results also show that when there is an electron-rich substituent in the 3-position, however, the reaction is either not selective and/or very slow.



As discussed previously, the fluorination reaction (or fluoro-deboronation) is thought to proceed via an *ipso* substitution of the boronic acid group, which forms the arylfluoride. This transformation is believed to proceed via boron activation followed by an *ipso* displacement mechanism.⁸⁸ This reaction has been shown to work best when there is an electron-rich substituent in the 4-position, but can work when there is an electron-rich substituent in the 2-position.

Alternatively, the fluoro-deboronation of di-substituted electron-rich arylboronic acid derivatives gave no selectivity, with multiple fluorinated isomers being observed. The fluoro-deboronation of substrates containing an electron-donating (OMe) and electron-withdrawing group (CHO) was also shown to be possible in the case of **131**. This is the first known example of the fluoro-deboronation reaction where the arylboronic acid derivative contains an electron-withdrawing group and where no metal catalyst is required.

The fluoro-deboronation of heterocyclic trifluoroborates, such as quinolines (**151**) and electron-rich pyridines (**145** and **147**), was also shown to be possible with conversion from the starting material only reaching a maximum of 50 %, although no proto-deboronated by-product was observed (Scheme 89). Products were isolated by brine

wash for removal of the unconverted boronic acid derivatives as no proto-deboronated products were formed.



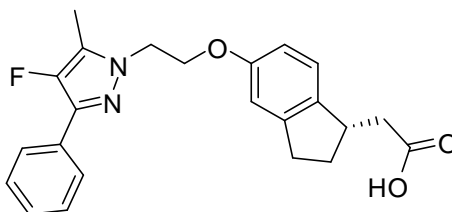
Scheme 89: Fluoro-deboronation of electron-rich pyridine boronic acid derivatives

Although the fluoro-deboronation reaction has been shown to be successful for both the synthesis of aryl- and heterocyclic fluorides, more work must be carried out to understand the fluoro- and proto-deboronation mechanism more fully. Once this is understood it is hoped that higher yields could be achieved with more complex arylfluorides being made accessible.

Step-wise Synthesis of 4-Fluoropyrazole Systems

4.1 Introduction

As mentioned in Chapter 1, methods of placing fluorine selectively on heterocyclic systems are of significant interest since these derivatives often exhibit bioactivity. For example, pyrazoles are a particular class of compounds used in the pharmaceutical and the agrochemical industry. 4-Fluoropyrazoles derivatives can be seen in drugs, although there are fewer examples of these than their non-fluorinated analogues, due to a lack of fluorination methodologies. An anti-diabetic drug⁸⁹ from Bayer (**165**) shows that di-substituted 4-fluoropyrazoles are potentially interesting derivatives in drug design.

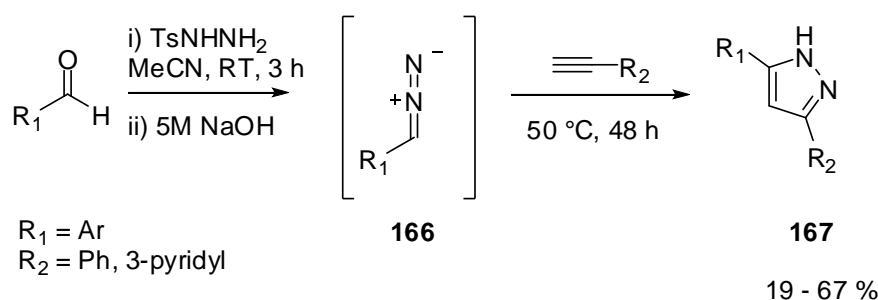
**165**

4.1.1 Synthesis of Pyrazoles

There are many methods for the synthesis of pyrazoles, many of which can be found in a review by Makino.⁹⁰ Some of the most useful examples, however, will be explained in more detail below.

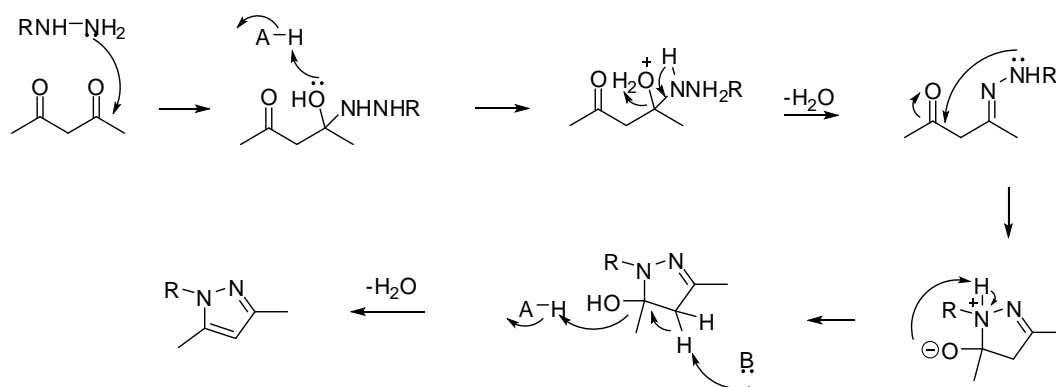
Pyrazoles can also be synthesised via 1,3-dipolar cyclo-additions of diazo compounds.⁹¹ This is a popular approach, although preparation and handling of the diazo compounds, which are known to be toxic and potentially explosive, is difficult. Recently, however, a new method for generating the aryldiazomethanes (**166**), from stable tosylhydrazone derivatives (Scheme 90), has been established as a safe alternative to handling aryldiazomethanes.⁹² This method allows for the synthesis of

regio-isomers, although the desired 3,5-disubstituted pyrazole (**167**) is usually obtained in very high selectivity (> 97:3) over the 3,4- disubstituted pyrazole.



Scheme 90: Synthesis of pyrazoles from 1,3-dipolar cyclo-additions of diazo compounds

The best method for the synthesis of pyrazoles is the direct condensation of 1,3-diketones and hydrazines as shown in Scheme 91. The condensation reaction is the most simple and straightforward procedure for their synthesis and can be catalysed by sulfuric acid. This method has a wide scope because of the readily availability of 1,3-diketones and also because one carbonyl of the diketone starting material can be replaced by an acetal, a hemi-acetal, a chlorovinyl group etc.⁹³



Scheme 91: Condensation of 1,3-diketone and hydrazine to give pyrazole

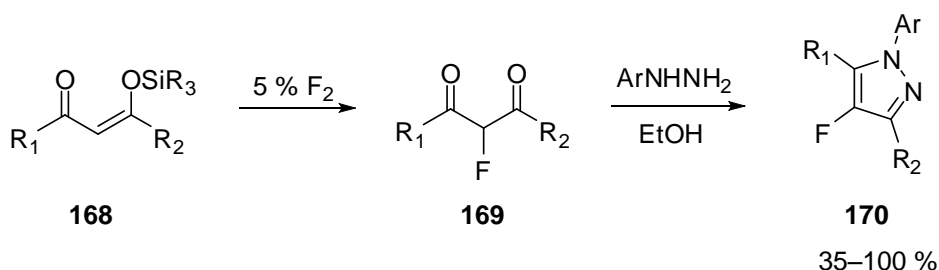
4.1.2 Step-wise Synthesis of 4-Fluoropyrazoles

There are very few examples of fluorination of pyrazoles directly on the pyrazole ring, as discussed in Chapter 1, and so most reported 4-fluoropyrazole syntheses use a

building-block approach, where the fluorine atom is incorporated early in the synthetic process.

4.1.2.1 Synthesis of 4-Fluoropyrazoles from 2-Fluoro-1,3-diketones

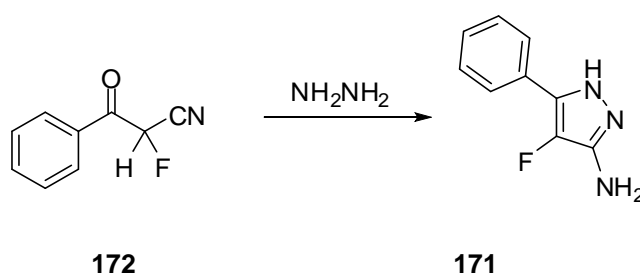
The synthesis of 4-fluoropyrazoles has been demonstrated by Bumgardner, where silyl enol ethers (**168**) are fluorinated and the resulting 2-fluoro-1,3,-diketone (**169**) reacted with arylhydrazines to afford the desired pyrazole product (**170**) in high yield (Scheme 92).^{94, 95} When unsymmetrical fluoro-diketone are used, a mixture of regio-isomers can be observed, although, the regioisomer obtained is the one expected on the basis that nucleophilic attack occurs at the more electrophilic carbonyl.



Scheme 92: *Synthesis of 4-fluoropyrazoles*

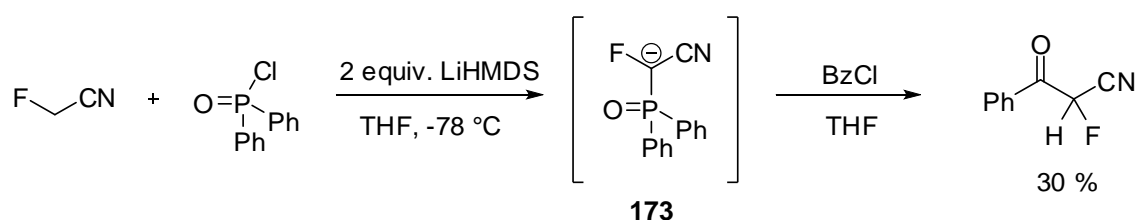
4.1.2.2 Alternative Syntheses of 4-Fluoropyrazoles

A recent building-block method for the synthesis of fluoropyrazoles derivatives is the reaction of benzoylfluoroacetonitrile and hydrazine to afford novel 4-fluoroaminopyrazoles, (**171**) (Scheme 93). However, the main disadvantage of this method is the difficulty in synthesising the benzoylfluoroacetonitrile starting material (**172**).



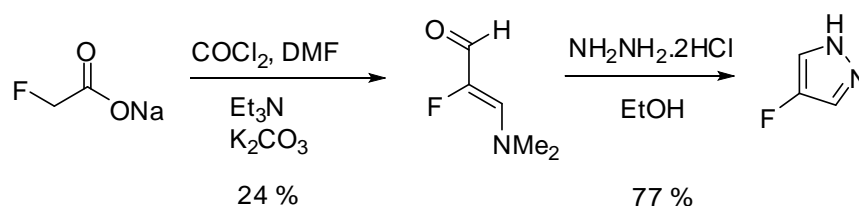
Scheme 93: *Synthesis of 4-fluoroaminopyrazoles*⁹⁶

The best conditions for the synthesis of **172** requires the preparation of the (diphenylphosphinoyl)fluoroacetonitrile anion, **173**, *in situ*, from fluoroacetonitrile and diphenylphosphinyl chloride⁹⁷ but this requires several steps and, furthermore, fluoroacetonitrile is very toxic (Scheme 94). Although this synthesis yields medicinally interesting substrates, other, safer methods for the synthesis of 4-fluoropyrazoles are required.



Scheme 94: Synthesis of benzoylfluoroacetonitrile

Also, a publication by Pfizer shows the synthesis of 4-fluoropyrazole which requires several steps, as well as the use of phosgene and has a poor overall yield (Scheme 95).⁹⁸



Scheme 95: Synthesis of 4-fluoropyrazole

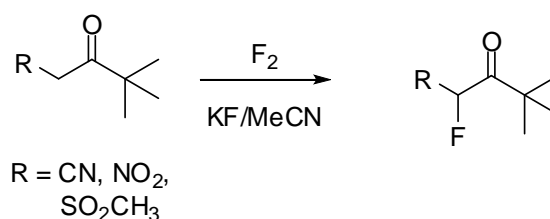
4.1.3 Synthesis of 2-Fluoro-1,3-diketones

There are a variety of methods for the fluorination of 1,3-diketones including by direct fluorination, where elemental fluorine is used as the electrophilic fluorinating agent and N-F compounds which will both be discussed in further detail below, as well as *via* fluorination of the silyl enol ether.⁹⁹

4.1.3.1 Synthesis of 2-Fluoro-1,3-diketones Using Elemental Fluorine

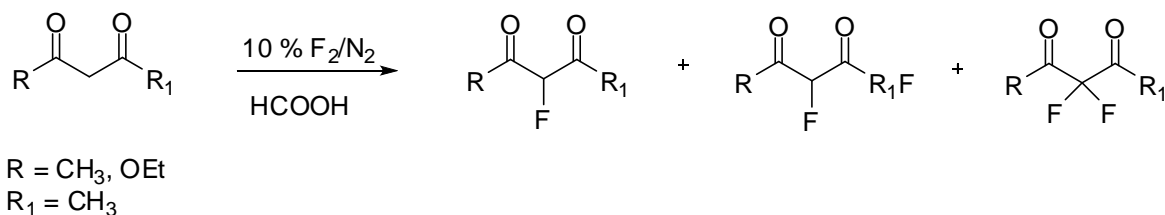
In order to synthesise fluoropyrazoles by step-wise methods, fluorodiketones must be prepared. Previously, direct fluorination had been used to only a limited extent in reactions with carbonyl compounds and this was usually at low temperatures (-78 °C).

Different carbonyl compounds are not equally reactive towards fluorine as the ease of fluorination depends on the nature and proximity of other functional groups. Fluorination must be carried out in conditions that enhance enol formation by base catalysis, metal catalysis or deprotonation of α -hydrogen atoms.¹⁰⁰ For example, fluorination of carbonyl systems bearing strong electron withdrawing groups at the α -position can occur when an excess of basic potassium fluoride is added as a suspension in acetonitrile solution (Scheme 96).¹⁵



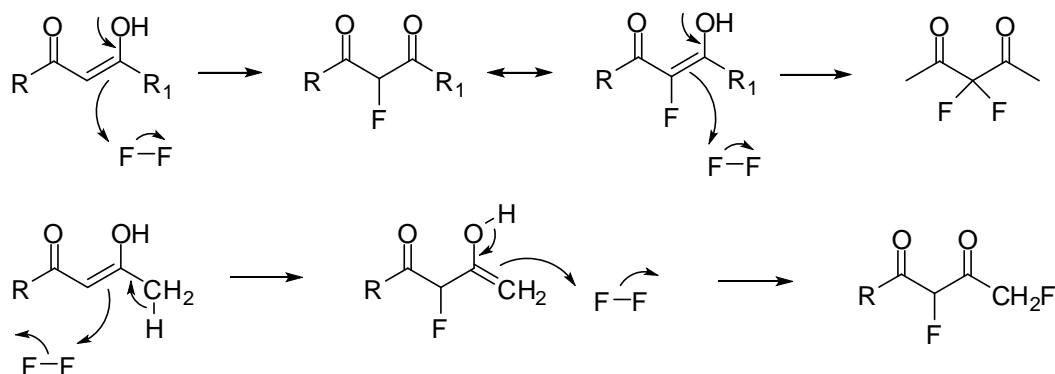
Scheme 96: Fluorination of carbonyl systems bearing electron-withdrawing groups

The fluorination of 1,3-diketones has been shown by various research groups. Chambers *et al*¹⁰¹ have demonstrated that elemental fluorine can be used as the fluorinating agent when formic acid is employed as the solvent (Scheme 97). Yields between 60–90 % can be achieved with up to 90 % conversion. It was found that the 1,3-diketones were more reactive than their corresponding esters, whereas di-esters failed to react.



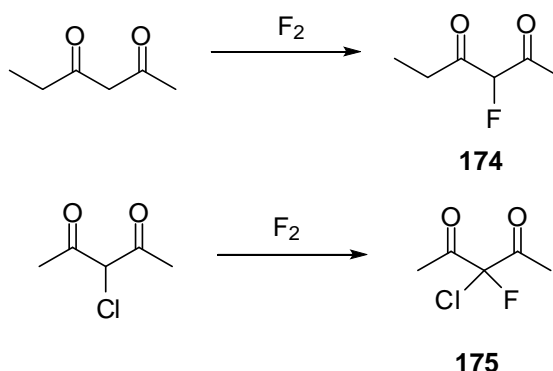
Scheme 97: Fluorination of 1,3-diketones with elemental fluorine

In all reactions a small amount of the difluorinated derivatives are afforded but these are easily removed from the desired product. Mono-fluorinated compounds do not readily enolise and consequently the rate of di-fluorination is very much slower than that of mono-fluorination thus the yield of difluorinated products is low. It was found that two mechanisms occur simultaneously to yield both difluorinated products (Scheme 98).



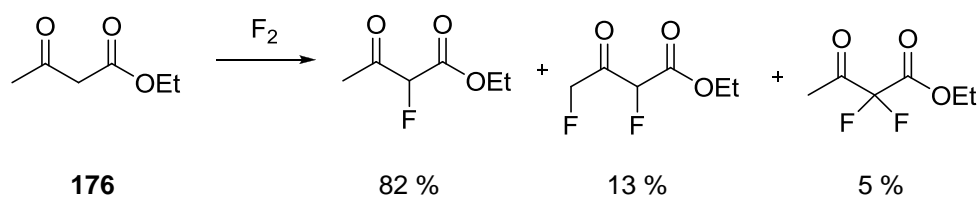
Scheme 98: Mechanism of di-fluorination of 1,3-diketones

Substrates which have a high initial equilibrium enol concentration in the solvent and/or rapidly convert from the keto to the enol form, such as hexane-2,4-dione **174**, will react quickly and selectively with fluorine to give mono-fluorinated products in high yield and high conversion. Conversely, substrates that have low enol concentrations and slow exchange rates, such as 3-chloropentane-2,4-dione **175**, give low conversions and yields of the desired mono-fluorinated products (Scheme 99).²⁸



Scheme 99: Fluorination of 1,3-diketones using elemental fluorine

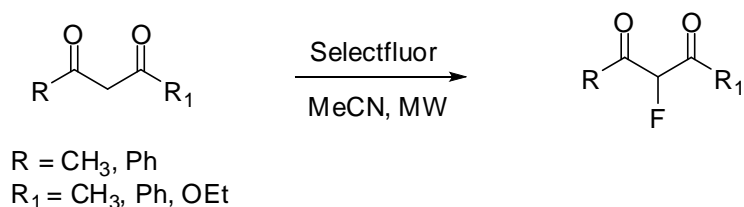
The fluorination of 1,3-diketones has also been carried out using flow reactor technology. A comparison between fluorination reactions of ethyl acetoacetate (**176**) (Scheme 100) using conventional batch and flow reactor conditions indicates that similar conversions and yields of desired products are obtained (for batch, 100 % conversion, 70 % yield; microreactor, 100 % conversion, 69 % yield) but the advantages of using flow reactors is seen in the continuous operation, faster reaction times and lower quantities of solvent required for efficient synthesis.¹⁰⁰



Scheme 100: Fluorination of ethyl acetoacetate

4.1.3.2 Synthesis of 2-Fluoro-1,3-diketones Using Selectfluor

Selectfluor has also been used for the electrophilic fluorination of 1,3-diketones. The reaction can be performed using microwave irradiation which can reduce reaction times from hours to 15 minutes (Scheme 101).



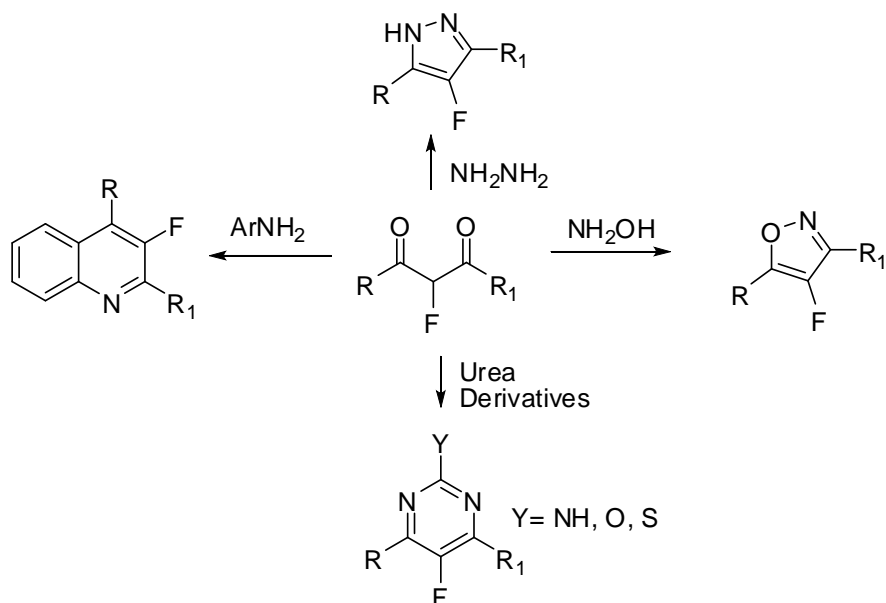
Scheme 101: Fluorination of 1,3-diketones using Selectfluor

Yields of 70–88 % were obtained with a small amount of the difluorinated by-products also being afforded. These difluorinated product could be isolated when two equivalents of Selectfluor were used.¹⁰² Although this is a fast reaction with good yields, Selectfluor is expensive and is not a good reagent for large scale syntheses, which may be required for the pharmaceutical industry.

4.2 Aims and Objectives

4.2.1 Synthesis of 4-Fluoropyrazoles

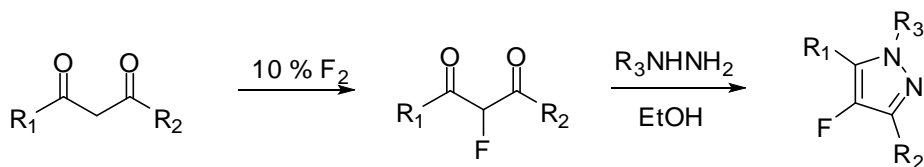
As discussed previously, convenient routes to fluorinated heterocycles are of on-going interest. Direct fluorination of heterocycles is very difficult and so building block synthesis strategies using fluorinated 1,3-dicarbonyl systems have often been employed as discussed above and shown in Scheme 102.



Scheme 102: Preparation of heterocycles from selectively fluorinated 1,3-diketones⁹⁵

The synthesis of 2-fluoro-1,3-diketones, using direct fluorination techniques, has been demonstrated by the Durham group and since 1,3-diketones have been used as starting materials for heterocyclic synthesis it was thought that fluorinated 1,3-diketones could be used as building blocks for synthesising a range of pharmaceutically relevant 4-fluoropyrazoles.

A range of fluoro-1,3-diketones will be synthesised using elemental fluorine and 1,3-diketones and a flow reactor, as discussed in Chapter 1. The fluoro-1,3-diketones will then be reacted with hydrazines, $RNHNH_2$, where $R = H$ and $R = Ph$, in ethanol to form a variety of 4-fluoropyrazoles (Scheme 103).



Scheme 103: Synthesis of 4-fluoropyrazoles from 2-fluoro-1,3-diketones

Studies concerning the synthesis of 4-fluoropyrazoles using a two-step continuous flow process where the entire pyrazole synthesis will be carried out using a flow reactor in

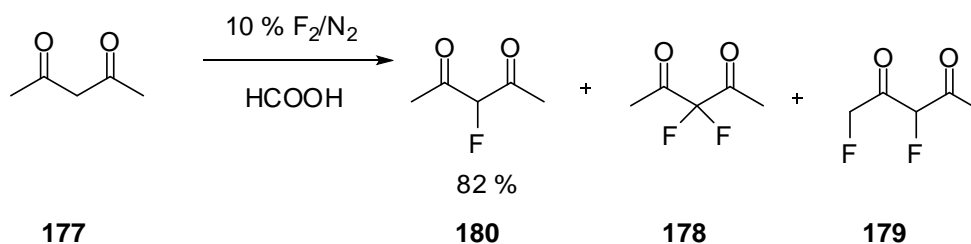
one process. This would allow faster and more efficient pyrazole synthesis that reduces solvent use and permit scale-out to be carried out quickly and easily.

4.3 Results and Discussion

4.3.1 Direct Fluorination of 1,3-Diketones

4.3.1.1 Fluorination of Pentane-2,4-dione

The fluorination of pentane-2,4-dione (**177**) was carried out in the flow reactor. The ^{19}F NMR spectrum of the crude product showed the presence of di-substituted products, 3,3-difluoropentane-2,4-dione (**178**) and 1,3-difluoropentane-2,4-dione (**179**) as well as the desired mono-substituted product, 3-fluoropentane-2,4-dione (**180**) in ratio 97:3 (mono:di) (Scheme 104).



Scheme 104: Fluorination of pentane-2,4-dione using fluorine

The ^{19}F NMR spectrum of the crude product also showed the presence of the keto (-192 ppm) and enol (-174 ppm) form of the product (Figure 20), which is consistent with the literature.¹⁰³

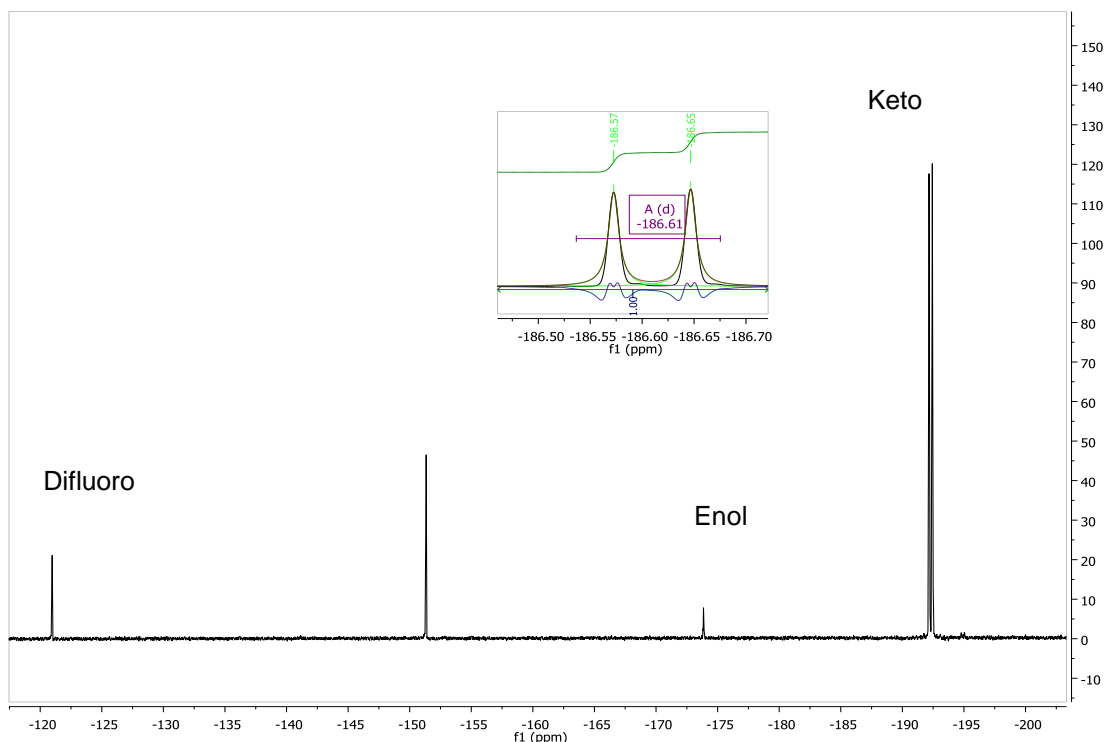


Figure 20: ^{19}F NMR spectrum from the fluorination of pentane-2,4-dione

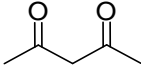
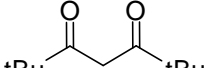
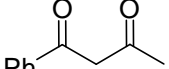
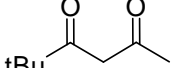
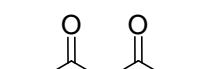
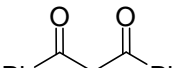
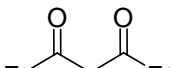
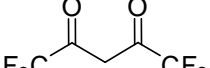
Attempts were made to reduce the quantity of di-fluorinated products formed. However, when the rate of fluorine addition was increased, di-fluorination increased and if the rate of addition was decreased, starting material remained, which was difficult to remove from the fluorinated products. The rate of addition was, therefore, a compromise between complete conversion from the starting material and di-fluorination. A range of solvents and reaction conditions were investigated to find the ideal conversion to **180**. The conditions which gave the best conversion to **180** (96 %), by GC, were 16 mmol fluorine gas (10 % F_2/N_2) added at the rate of 15 mL/ min over 4 hours and 4 mmol of **177** dissolved in 4 mL of solvent added at the rate of 1 mL/ h. This shows that the flow reactor is an efficient method for the synthesis of fluoro-1,3-diketones and so further examples of 1,3-diketones were fluorinated in the same manner.

4.3.1.2 Fluorination of Other 1,3-Diketones

A range of 1,3-diketones were fluorinated using the flow reactor. In all cases the desired fluorodiketone could be isolated and in most cases excellent yields could be obtained.

Table 14: Fluorination of 1,3-diketones

Continuous flow reactor
 $10 \text{ F}_2/\text{N}_2 \text{ 15 mL/min}$
 HCOOH, 4 h

1,3-Diketone	Conversion (GC-MS)/ %	Mono-: di-fluoro (^{19}F NMR)	Product	Isolated Yield/ %
 177	95	97:3	180	82
 181	97%	99:1	188	85
 182	96	92:8	189	89
 183	96	91:1	190	87
 184	96	97:1	191	84
 185	70	97:3	192	55
 186	89	99:1	193	83
 187	-	-	-	-

The best yields were obtained when a small amount (~5 mL) of solvent was used. In the case of **185**, however, 20 mL of solvent was used due to poor solubility of the

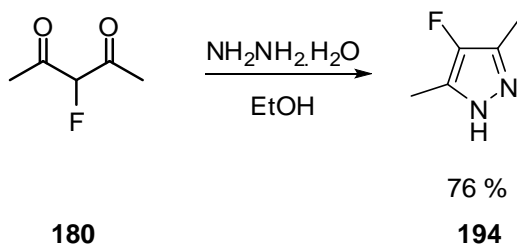
starting material, which resulted in a lower conversion (70 %) for the reaction. The amount of fluorine was increased (up to 20 mL/ min) but this only increased the ratio of difluorinated material and did not improve the conversion to the mono-fluorinated product.

For **187** no clean reaction occurred and, instead, a complex mixture of products was obtained. This is due to **187** containing highly electron-withdrawing trifluoromethyl groups, making the system less nucleophilic, and a low enol content.

Table 14 shows that the direct fluorination reaction is an efficient method for the synthesis of fluoro-1,3-diketones. Excellent yield can be achieved when 1,3-diketones with a high enol content and which contain at least one electron-donating group.

4.3.2 Synthesis of 4-Fluoropyrazoles From Fluoro-1,3-diketones

4.3.2.1 Synthesis of 4-Fluoro-3,5-dimethylpyrazole



Scheme 105: *Synthesis of 4-fluoro-3,5-dimethylpyrazole*

Fluorodiketones have a distinctive doublet at -185 to -190 ppm, with a doublet of ~ 50 Hz, while fluoropyrazoles have a singlet in the range -170 and -180 ppm which allows the reaction to be monitored easily by ^{19}F NMR spectroscopy (Figure 21). After full conversion to the desired product, and standard work-up of the reaction, the pure 4-fluoro-3,5-dimethylpyrazole (**194**) could be obtained easily from recrystallisation or column chromatography.

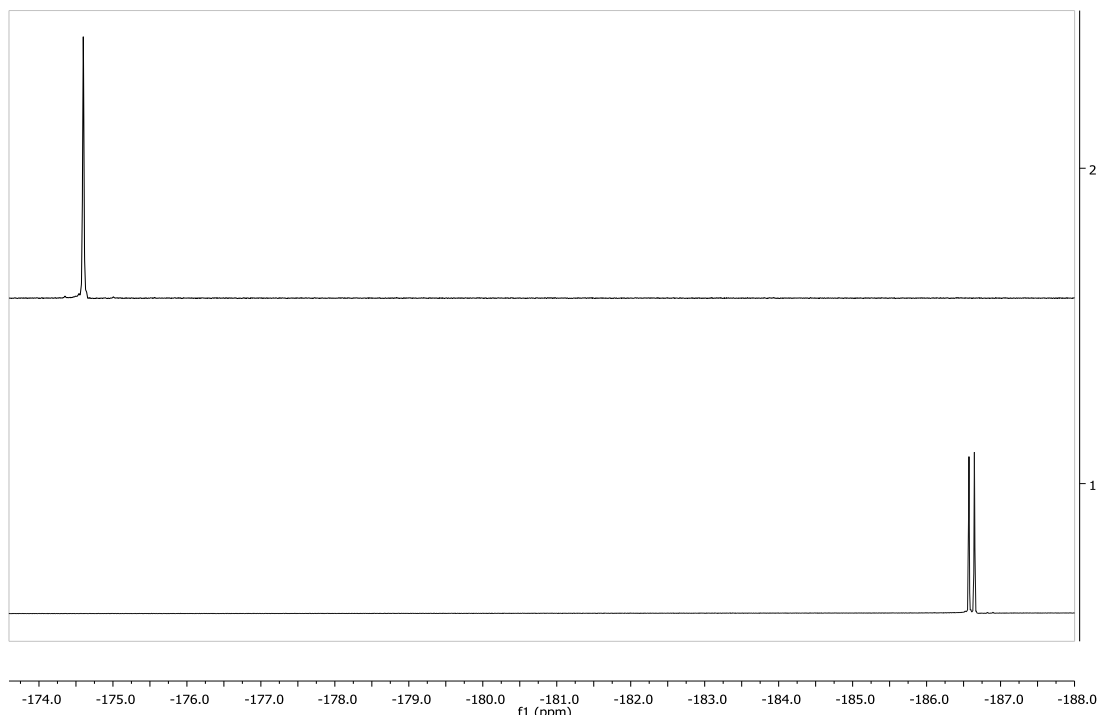


Figure 21: ^{19}F NMR signals of fluorodiketones and 4-fluoropyrazoles

The X-ray crystal structure of **194** was obtained to confirm the molecular structure and confirm the position of the fluorine atom at the 4-position on the heterocyclic ring (Figure 22).

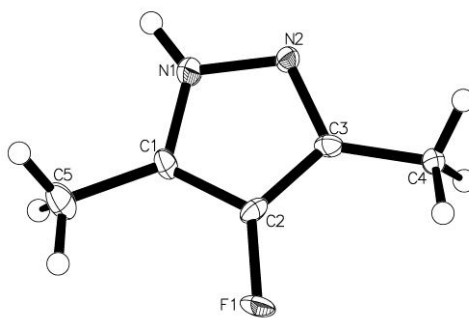


Figure 22: X-ray crystal structure of 4-fluoro-3,5-dimethyl pyrazole (**194**)

4.3.2.2 Synthesis of Further 4-Fluoropyrazoles

Since the hydrazine condensation reaction was shown to be very effective in the synthesis of **194**, the same method was used to synthesise a range of 4-fluoropyrazoles from their corresponding fluorodiketones with hydrazine monohydrate and phenyl hydrazine, using the same conditions described. All reactions were followed by ^{19}F

NMR spectroscopy and GC-MS and fluoropyrazoles products were purified by recrystallisation or column chromatography.

Table 15: *Synthesis of 4-fluoropyrazoles*

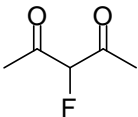
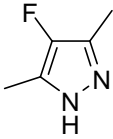
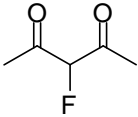
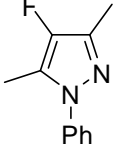
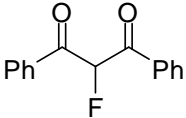
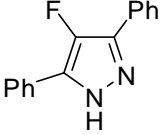
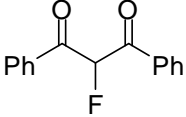
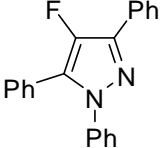
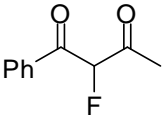
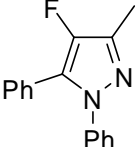
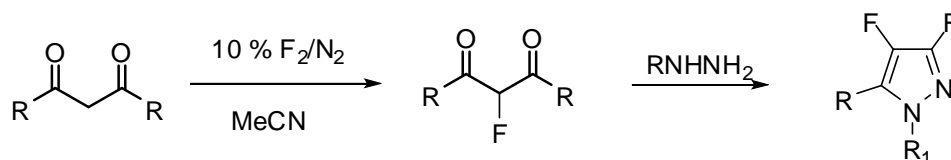
$ \begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{R}-\text{C}-\text{C}-\text{R}_1 \\ \\ \text{F} \end{array} \xrightarrow[\text{EtOH, reflux}]{\text{R}_2\text{NHNH}_2} \begin{array}{c} \text{F} \quad \text{R}_1 \\ \diagup \quad \diagdown \\ \text{C}=\text{C} \\ \diagdown \quad \diagup \\ \text{N}-\text{N} \\ \\ \text{R}_2 \end{array} $				
Fluoro-1,3-diketone	Hydrazine	Product	Conversion (GCMS)/ %	Isolated Yield/ %
 177	NH ₂ NH ₂ ·H ₂ O	 194	100	79
 177	PhNHNH ₂	 195	100	73
 185	NH ₂ NH ₂ ·H ₂ O	 196	100	79
 185	PhNHNH ₂	 197	100	83
 182	PhNHNH ₂	 198	100	84

Table 15 shows that the synthesis of 4-fluoropyrazoles, from their corresponding fluorodiketone starting materials, is a very effective reaction, although two synthetic steps have to be carried out to obtain the 4-fluoropyrazole from the parent diketone and

hydrazine substrates. In some reactions purification must also be carried out at each synthetic step which increases the reaction time and solvent requirements of the reaction. It was thought that a more environmentally friendly method could be designed where both synthetic steps could be carried out sequentially with no need for isolation of the intermediate fluorodiketone.

4.3.3 Flow Reactor Synthesis of 4-Fluoropyrazoles

The reaction of **177** with hydrazine monohydrate was repeated without purification of the fluoro-1,3-diketone intermediate to see if purification was necessary to afford **194** in good yield and to increase the speed of the synthesis (Scheme 106).



Scheme 106: Synthesis of 4-fluoropyrazoles using 2-step process

The reaction proceeded well without purification of the intermediates since the fluorination step generally gives a very high conversion from the starting material to the fluorodiketone with very little difluorinated by-products afforded. The fluoro-1,3-diketone was then reacted with hydrazine monohydrate to yield the 4-fluoropyrazole derivative in excellent yield. If the conversion of the fluorination step was poor then a significant quantity of the non-fluorinated pyrazole, which is difficult to separate from the 4-fluoropyrazole, was obtained.

Since the reaction was possible without purification of the fluoro-diketone intermediates, it was proposed that the reaction could be carried out completely using a flow reactor setup where a high yielding fluorination step could be followed by the cyclisation upon addition of hydrazine.

A range of 1,3-diketones and hydrazines were investigated to see if fluoropyrazole systems can be synthesised in a single flow process. Very soluble (i.e. liquid) 1,3-diketones, such as **177** and 2, 2, 6, 6-tetramethyl-3, 5-heptanedione (**181**) were

explored as these only require a small amount of solvent (< 5 mL) and give high conversions compared with > 20 mL for the crystalline **185**. Reactions of various hydrazines were also examined, including hydrazine monohydrate, methyl hydrazine and phenyl hydrazine. Hydrazine is miscible with water and alcohols but barely miscible with hydrocarbons. Both water and ethanol were, therefore, investigated as suitable solvents. Phenyl hydrazine is, however, not soluble in water and so acetonitrile was used as the reaction media.

4.3.3.1 Test Reaction – Fluorination of Pentane-2,4-dione and Cyclisation Using Hydrazine Monohydrate

A method was proposed where the reactor was set up as above but with the addition of a T-piece, where hydrazine could be added *via* a mechanised syringe pump as shown in Figure 23. This would potentially allow efficient mixing of the hydrazine and fluoro-1,3-diketone in PTFE tubing and therefore higher conversion to the 4-fluoropyrazole.

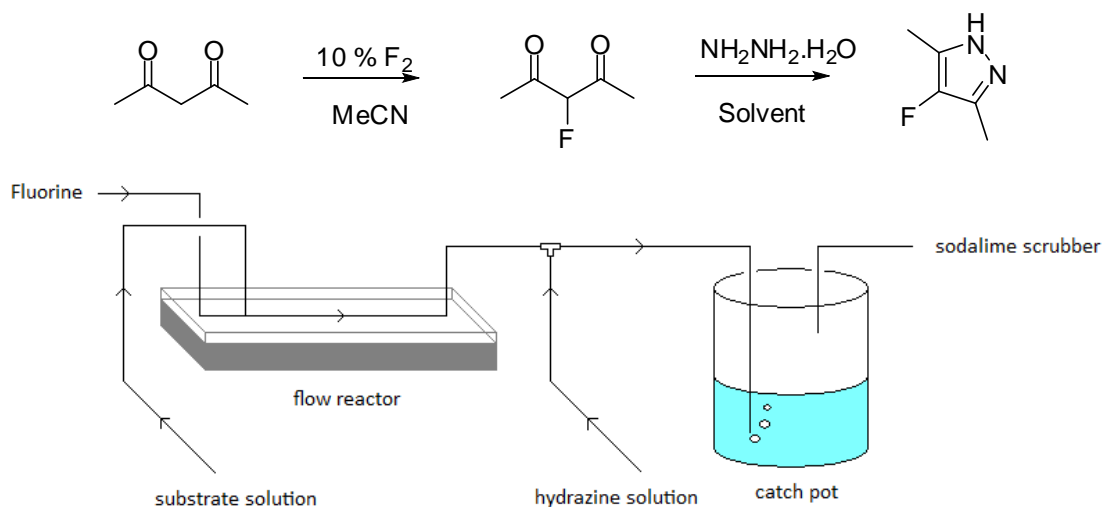


Figure 23: Continuous flow reaction setup

In this setup, 1 mmol of the **177** was diluted in 4 mL of acetonitrile and 1.2 mmol of hydrazine hydrate was dissolved in 4 mL of solvent (acetonitrile, ethanol or water). Both solutions were added at the rate 2 mL/ min using a mechanised syringe pump. 10 % F₂/N₂ was added at the rate 18 mL/ min (an excess) to ensure full conversion to **194** occurred and, consequently, efficient synthesis to the 4-fluoropyrazole. Although the excess fluorine may produce some difluorinated material, this does not react with the

hydrazine and can be removed easily. Conversely, non-fluorinated pyrazole is very difficult to separate from the 4-fluoropyrazole.

Initial investigations showed that some **177** remained when only 1.2 equivalents of the hydrazine was used. The reaction was, therefore, repeated with 1.5 equivalents of the hydrazine and this ensured almost complete conversion from **177** to **194**, with only difluorinated material as a by-product. Product **177** was isolated as previously in 74 % yield. These conditions gave the best conversion to **194** and so were used in subsequent reactions with different 1,3-diketones and hydrazines.

4.3.3.2 Flow Synthesis of Other Fluoropyrazoles

Since the reaction of **177** and hydrazine using the flow reactor was successful, a range of 4-fluoropyrazoles were synthesised using the same method as above. Since the flow reaction depends on high conversion of the first fluorination step, reactions were only carried out on 1,3-diketones that gave > 95 % conversion, to the fluoro-1,3-diketone, from the starting materials due to the likelihood of non-fluorinated pyrazoles forming. When the flow reaction was complete, ^{19}F NMR spectroscopy was carried out (Figure 24).

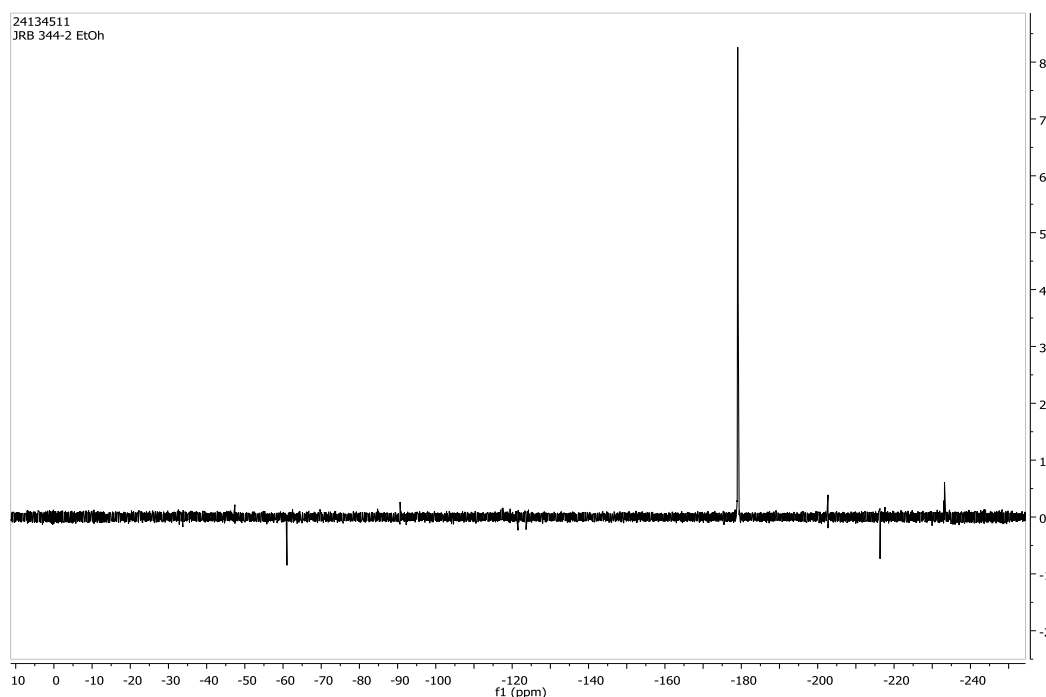


Figure 24: An example of a reaction mixture ^{19}F NMR spectrum

Conversion to the 4-fluoropyrazole can be clearly shown by the presence of a singlet between -170 ppm and -180 ppm, depending on the pyrazole synthesised. Any unreacted fluoro-1,3-diketone could be seen as a doublet at around -190 ppm (keto) or as a singlet at around -165 ppm (enol). All values were compared to a pure sample or the literature, where possible.

GC-MS was carried out to ensure no non-fluorinated pyrazole was obtained. After confirmation that the reaction was complete, the reaction mixture was then worked up from DCM and the product passed through a silica plug to remove tar that was formed during the reaction. The product was then purified by recrystallisation or column chromatography. The results of the flow reactions can be seen in Table 15.

It can be seen from Table 16 that the 2-step sequential flow method is viable for the synthesis of 4-fluoropyrazoles. The conversions are excellent in cases where the condensation reaction took place. The reaction did not proceed in the cases where bulky hydrazines were used in conjunction with bulky diketones (Runs 9–10). The mechanism of the pyrazole synthesis depends on the attack of the nucleophile at the carbon bond and if this is obstructed by sterically demanding groups (e.g. tertiary butyl), it is difficult for a relatively bulky methyl or phenyl hydrazine to attack. In these cases the reactions were repeated using the standard step-wise process where the diketone is fluorinated and purified and then reacted with the hydrazine at reflux overnight in ethanol. After 3 days stirring at reflux, very little 4-fluoropyrazole derivative was present, instead only fluoro-diketone and fluoro-enol remained. This shows that the 2-step flow procedure follows the results found in the standard step-wise process.

Table 16: Continuous flow synthesis of fluoropyrazoles

One step flow process

Run	Diketone	Hydrazine	Hydrazine Solvent	Product	Isolated Yield/ %
1 2	R/R ₁ = CH ₃	NH ₂ NH ₂ .H ₂ O	H ₂ O EtOH	194	66 74
3 4 5	R/R ₁ = CH ₃	MeNHNH ₂	MeCN H ₂ O EtOH	 199	73 83 88
6 7	R/R ₁ = CH ₃	PhNHNH ₂	MeCN EtOH	195	67 81
8	R/R ₁ = ^t Bu	NH ₂ NH ₂ .H ₂ O	EtOH	 200	74
9	R/R ₁ = ^t Bu	MeNHNH ₂	EtOH	-	No reaction
10	R/R ₁ = ^t Bu	PhNHNH ₂	EtOH	-	No reaction
11	R = CH ₃ R ₁ = Ph	NH ₂ NH ₂ .H ₂ O	EtOH	 201	69
12	R = CH ₃ R ₁ = ^t Bu	NH ₂ NH ₂ .H ₂ O	EtOH	 202	71
13	R = Ph R ₁ = ^t Bu	NH ₂ NH ₂ .H ₂ O	EtOH	 203	64
14	R/R ₁ = Et	NH ₂ NH ₂ .H ₂ O	EtOH	 204	72

Conditions = 1 mmol substrate in 4 mL solvent added at 0.5 mmol/ h. 1.2 mmol hydrazine in 4 mL solvent added 0.6 mmol/ h, 18 mL/ min F₂/N₂ (excess)

The initial reactions (Runs 1–7) were all carried out using multiple solvent systems to see which gave the best results. The results clearly show that ethanol is the best solvent for the condensation step and so this was used in further reactions (Run 8–14).

Again the structure of the isolated compounds could be proven by X-ray crystallography. Figure 25 shows the structure of **200**, where the fluorine atom is clearly shown at the 4-position of the heterocyclic ring.

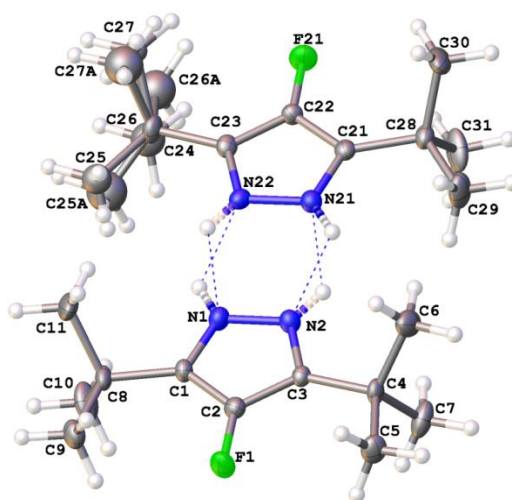


Figure 25: *Crystal structure of 3,5-di-tert-butyl-4-fluoro-1H-pyrazole (200)*

These results show that the synthesis of 4-fluoropyrazoles can be carried out using a continuous gas/liquid – liquid/liquid flow process. The yields are comparative to those achieved using a two-step process but the reaction time is considerably lower and heating is not required.

4.4 Conclusions

The synthesis of fluoro-1,3-diketones, using the flow reactor, was accomplished, with high conversion and yields being obtained. In most cases a small amount (< 5 %) of difluorinated product was also observed but the fluorodiketones could be used, without purification, for further reactions.

The step-wise 4-fluoropyrazole synthesis, where the fluoro-1,3-diketone is synthesised in ~ 85 % yield and then reacted with the hydrazine at reflux, can afford the desired

product in > 95 % yield. This is a useful method for the synthesis of 4-fluoropyrazoles, with excellent yield and purity being achieved in all cases.

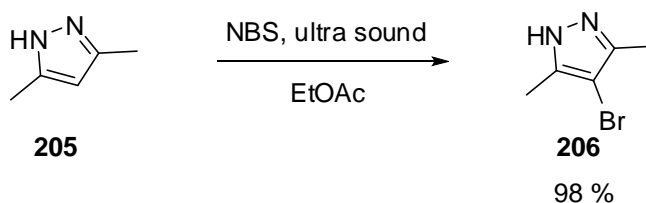
Alternatively, the continuous flow procedure can afford the desired product in approximately 70 % yield, with no need for heating and only a two hour reaction time. This reduces the number of purification steps required, thus making the reaction faster, cheaper and more environmentally friendly since considerably less solvent is required. This represents the first examples of a sequential continuous flow gas/liquid – liquid/liquid process involving direct fluorination in the first stage of a multi-step flow process. The reaction can be used with many different 1,3-diketones, as long as the fluorination of these is selective and efficient. A range of hydrazines can also be used except in the cases where the 1,3-diketone contains large steric bulk. This work has been published.¹⁰⁴

Ring Fluorination of Pyrazoles

5.1 Introduction

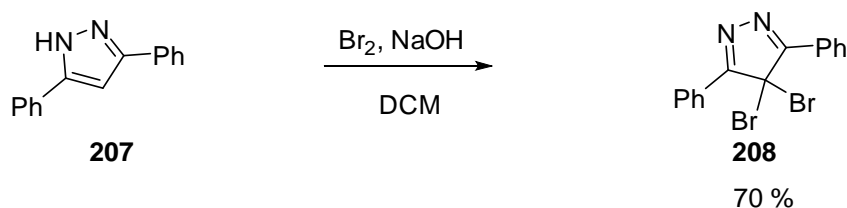
There are many examples of the synthesis of fluorinated 6-membered heterocyclic rings, such as fluoro-pyridine, -pyrimidine and -quinoline systems, processes for the preparation of corresponding fluorinated 5-membered aza-heterocyclic systems, such as fluorinated pyrroles and pyrazoles, are relatively rare. Building block strategies are often employed in the synthesis of fluorinated pyrazoles, as demonstrated and extended in Chapter 4.

However, for other halogenations, direct chlorination and bromination of pyrazoles has been demonstrated. Mono-bromination of di-substituted pyrazoles is possible when *N*-bromosuccinimide (NBS) or bromine water are employed as the electrophilic brominating agent (Scheme 107) whilst the analogous chlorination reaction is also possible when chlorine is used.¹⁰⁵



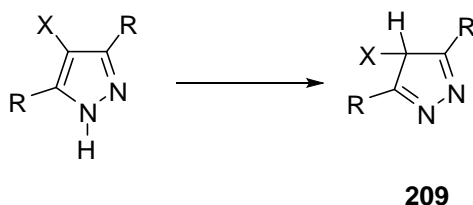
Scheme 107: Bromination of 3,5-disubstituted pyrazoles

It has also been shown that di-bromination of the pyrazole ring is possible to give the 4,4-dibromo-4H-pyrazole derivative (**208**) (Scheme 108). Both the mono-bromination and di-bromination reactions are fast and high yielding.¹⁰⁶



Scheme 108: Di-bromination of 3,5-disubstituted pyrazoles

The halogenation of pyrazoles, using chlorine and bromine in acetic acid, show a high propensity toward 1,3 migration where their 4H- form (**209**) persists (Scheme 109) due to the labile nature of the N–X bonds in the corresponding 1H-pyrazoles when halogenated in acetic acid.¹⁰⁷



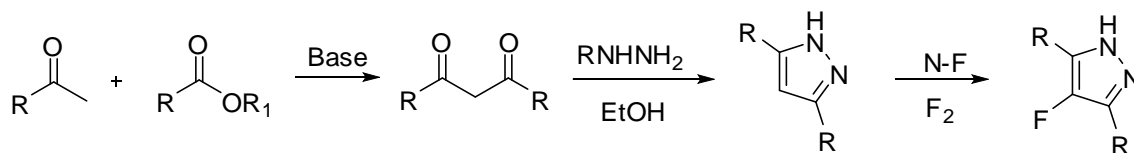
Scheme 109: *Synthesis of 4H-pyrazoles*

Although halogenations have been shown to be possible for bromine and chlorine, there has been no research carried out on the fluorination of pyrazoles in this manner. These results indicate that the fluorination of pyrazoles may be possible, using electrophilic N–F compounds and elemental fluorine, to give mono-fluorinated and di-fluorinated fluoropyrazoles in high yield.

5.2 Aims and Objectives

As shown in Chapter 4, fluorinated pyrazoles can be obtained through a 2-step process from the reaction of hydrazines and fluorinated 1,3-diketones. Although this is an excellent reaction and gives the desired pyrazole in good yield, it was thought that 4-fluoropyrazoles may be synthesised directly from the parent pyrazole in a similar manner to the fluorination of isoxazoles established by Stephens⁴². This could allow late stage fluorination to be carried out which is beneficial for the synthesis of fluorinated pharmaceutical targets.

Pyrazole substrates were either obtained from commercial suppliers or synthesised by reaction of the appropriate 1,3-diketone derivatives and hydrazine or phenyl hydrazine, heated to reflux in ethanol following literature procedures.⁹³ The pyrazoles were fluorinated using both Selectfluor™ and elemental fluorine to allow a comparison of the fluorinating agents reactivity. Reactions with Selectfluor™ were carried out using microwave irradiation to decrease the reaction times.



Scheme 110: Total synthesis of 4-fluoropyrazoles

Fluorination of pyrazoles with a variety of functional groups in the 3 and 5 position of the heterocyclic ring were investigated, including aryl groups with a range of substituents on the ring, to see if there is a trend in the reaction outcome. The fluorination of mono-substituted pyrazoles and 1H-pyrazole was also investigated to see if a fluorination of the ring is possible and, if so, if it is selective.

5.3 Results

5.3.1 Synthesis of 1,3-Diketones

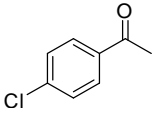
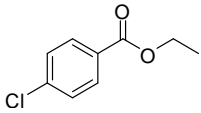
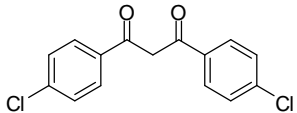
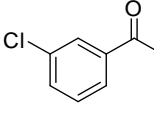
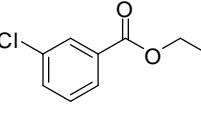
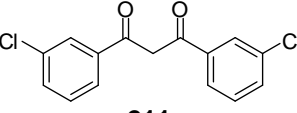
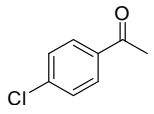
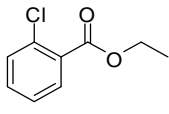
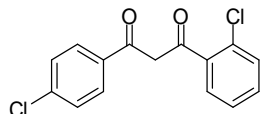
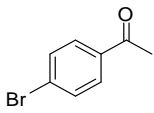
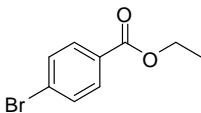
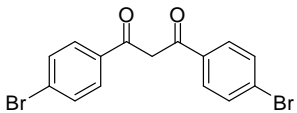
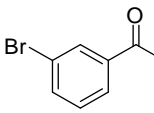
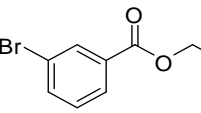
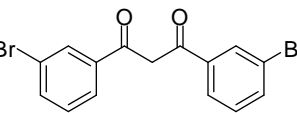
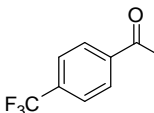
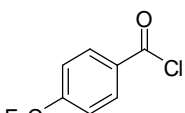
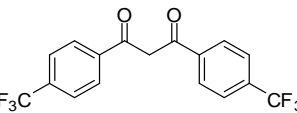
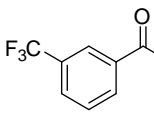
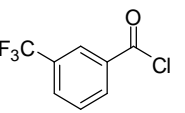
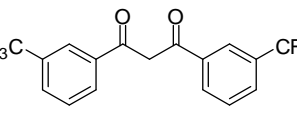
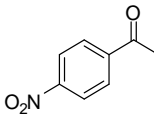
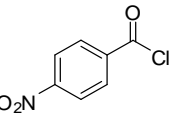
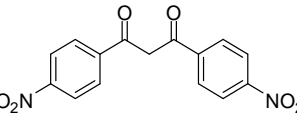
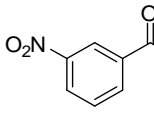
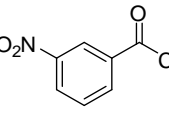
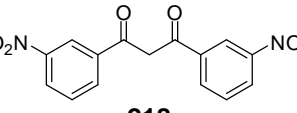
A range of *ortho*, *meta* and *para* substituted diaryl 1,3-diketone starting materials were synthesised from corresponding acetophenone and benzoate substrates using the mixed Claisen reaction (Scheme 111).



Scheme 111: Mixed Claisen reaction

The diaryl diketones were synthesised so that a comparative study of how electron-donating (OMe) and electron-withdrawing substituents (Cl, Br, CF₃, NO₂) on the phenyl ring affected the trend in the reactivity of the 3,5-diarylpyrazole with fluorine and Selectfluor™. The bromine and chlorine substituted derivatives were synthesised as these can be easily converted to other groups (e.g. coupling reaction to form C–C bond), which could be useful in the synthesis of more complex pharmaceutical targets (Table 17).

Table 17: *Synthesis of 1,3-diketones*

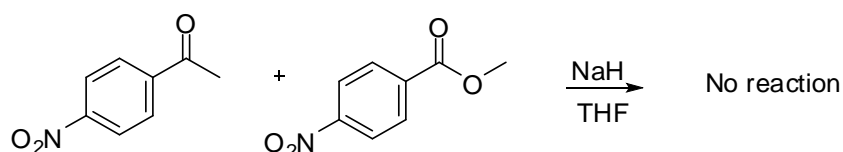
$ \text{R}-\text{C}_6\text{H}_4-\text{C}(=\text{O})\text{CH}_3 + \text{R}-\text{C}_6\text{H}_4-\text{C}(=\text{O})\text{OR} \xrightarrow[\text{THF}]{\text{Base}} \text{R}-\text{C}_6\text{H}_4-\text{C}(=\text{O})\text{CH}_2\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{R} $				
Ketone	Ester/acid chloride	Base	Product	Isolated Yield/ %
		NaH	 210	83
		NaH	 211	86
		NaH	 212	78
		NaH	 213	74
		NaH	 214	77
		NaH	 215	78
		NaH	 216	72
		LiHMDS	 217	76
		LiHMDS	 218	70

Initial experiments, with potassium *tert*-butoxide as the base in THF¹⁰⁸, failed to form the required enolate at various temperatures between 0 °C and reflux. The solvent was

then changed to DMF to aid solubility, which resulted in approximately 30 % yield but purification was found to be difficult due to remaining DMF.

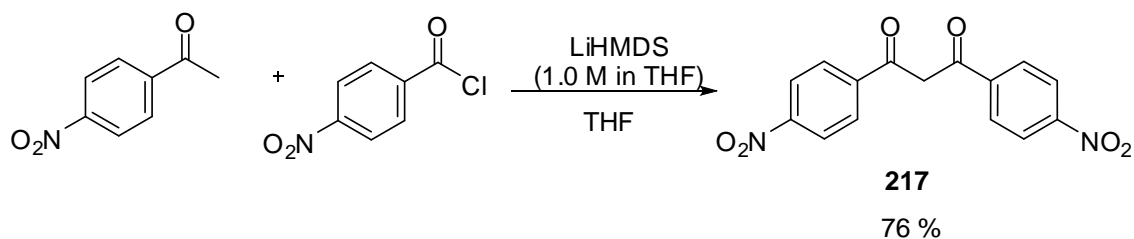
A stronger base was used which would allow THF to be used in place of DMF. Sodium hydride (60 % in mineral oil) was chosen which resulted in complete conversion to the 1,3-diketone and over 80 % isolated yields after recrystallisation. These reaction conditions effectively gave the chloro- and bromo- *meta* and *para* substituted derivatives. Alternatively, the trifluoromethyl- analogues (**215** and **216**) were synthesised using the more reactive acid chloride in place of the benzoate as this led to higher yields.

Reaction with the nitro- derivatives, however, did not yield the desired products (**217** and **218**) and so the reaction was repeated at 0 °C, room temperature and at reflux (Scheme 112). In all cases only starting material remained (by TLC and LC-MS). Changing the base to potassium carbonate and THF also resulted in only starting material after two days at reflux.



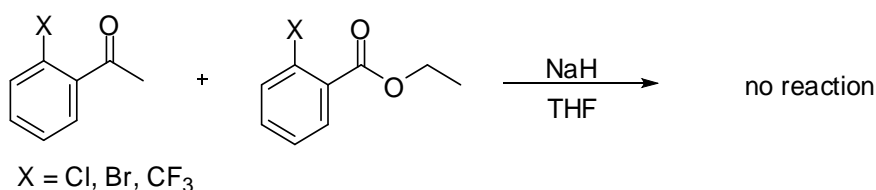
Scheme 112: *Synthesis of nitro- substituted phenyl diketones*

A stronger base, lithium bis(trimethylsilyl)amide (LiHMDS) as a 1.0 M solution in THF, was then used, and the more reactive acid chloride was used in place of the ester.¹⁰⁹ The base was dissolved in THF and left to stir at 0 °C for 10 min and the acetophenone then added. The acid chloride was subsequently added and the reaction left to stir at room temperature overnight. On quenching the reaction mixture with 30 % HCl, a pale yellow/brown precipitate formed which LC-MS indicated was the desired 1,3-diketone (Scheme 113).



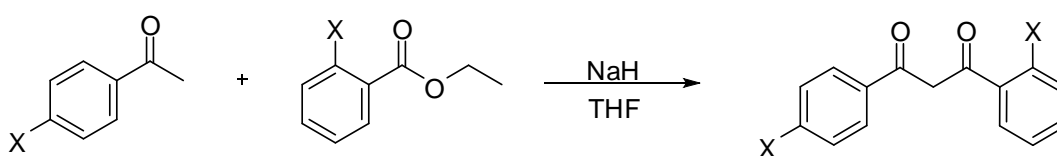
Scheme 113: Synthesis of nitrophenyl 1,3-diketone derivatives

In all *ortho* substituted cases, no reaction occurred under similar reaction conditions and the lack of reactivity was thought to be due to steric hindrance (Scheme 114).



Scheme 114: Reaction between *ortho*-substituted aryls

The reaction of a *para* substituted acetophenone and *ortho* substituted benzoate (Scheme 115), however, resulted in the desired 1,3-diketone, although the reaction took 3 h longer to complete indicating that the steric effect is only important when there are *ortho* substituents on both rings.



Scheme 115: Reaction between *ortho* and *para* substituted aryls

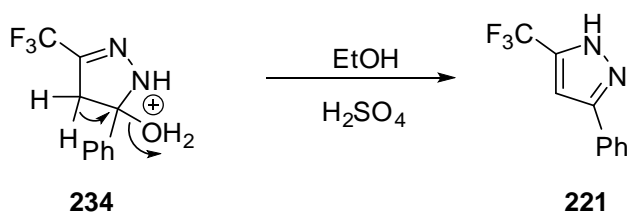
5.3.2 Synthesis of 3,5-Disubstituted Pyrazoles

With a range of 1,3-diketones in hand, the corresponding 3,5-disubstituted pyrazoles were synthesised, using the same method shown in Chapter 4. All were recrystallised and, where possible, the analytical data compared to the literature. Table 18 shows that the reaction is very efficient and high yielding. In all cases the reaction was complete after reflux overnight in ethanol.

Table 18: *Synthesis of 3,5-diarylpyrazoles*

Ketone	Product	Yield/ %	Ketone	Product	Yield/ %
177	 205	94	212	 227	76
182	 220	93	213	 228	85
219	 221	93	214	 229	88
177	 222	90	215	 230	88
185	 223	96	216	 231	80
185	 224	93	217	 232	79
210	 225	87	218	 233	96
211	 226	85			

In some cases, where an electron-withdrawing group was present, hydroxy-pyrazolines¹¹⁰ (an intermediate in the pyrazole synthesis) were observed, by TLC and mass spectroscopy (Scheme 116). This by-product could be prevented from forming by the addition of sulfuric acid (~ 0.5 mL) to the reaction mixture.



Scheme 116: Elimination of hydroxy-pyrazoline to pyrazole

For example, the reaction of 4,4,4-trifluoro-1-phenylbutane-1,3-dione (**219**) and hydrazine with no sulfuric acid present resulted in only the formation of the 5-phenyl-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-5-ol (**234**) but on addition of 0.5 mL of concentrated sulfuric acid, complete conversion to **221** was achieved.

5.3.3 Fluorination of Pyrazoles

For the reaction between 3,5-diarylisoxazoles and Selectfluor™, Stephens found that, although the desired 4-fluoroisoxazole was formed selectively, consumption of the starting material was always incomplete and only isolated yields of ~35 % could be achieved. However, Selectfluor™ was chosen as the fluorinating agent to start this investigation of fluorination of pyrazoles. The reaction will then be repeated using elemental fluorine to investigate whether direct fluorination of pyrazoles is possible.

When the 3,5-disubstituted pyrazole and one equivalent of Selectfluor™ in acetonitrile were heated together by microwave irradiation (90 °C, 20 minutes), the desired 3,5-disubstituted-4-fluoropyrazole could be obtained. Similarly, the fluorination was carried out using the batch fluorination process with elemental fluorine as a 10 % mixture in N₂ (30 mL/ min for 4 h) bubbled through a solution of the pyrazole in glacial acetic acid. All reactions followed by ¹⁹F NMR spectroscopy with a singlet between -170 and -185 ppm expected for the desired fluoropyrazoles product.

Table 19: Synthesis of 4-fluoropyrazoles using Selectfluor™ and F₂

Pyrazole	4-Fluoropyrazole	Isolated Yield Selectfluor™/ %	Isolated Yield Fluorine/ %
205	 194	-	-
220	 201	33	45
221	 235	43	46
222	 195	43	40

As with the fluorination of 3,5-diphenylisoxazoles, conversion to the 4-fluoropyrazoles was poor, with only 40–55 % being achieved although the reactions were clean, with very little by-products forming. Separation and purification of the mono-fluorinated pyrazole products from the starting material was difficult, but was achieved by column chromatography on silica gel or alumina. As can be seen in Table 19, the yields with Selectfluor and elemental fluorine were comparable, showing that both methods are useful reagents in the synthesis of fluoropyrazoles.

The fluorination of **205** was very inefficient due to extensive tar formation, likely from fluorination of the methyl groups and subsequent product degradation. Similarly, the

fluorination of **220** gave a lower yield due to the presence of the methyl group but the product could be isolated in 33 % yield.

The fluorination of pyrazoles where $R_1/R_2 = \text{CH}_3, \text{Ph}, \text{CF}_3$ and $R = \text{H}$ or Ph gave the 4-fluoropyrazole as expected but in each case conversion of only 50–60 % could be reached. The temperature and reaction time was increased but this did not lead to higher conversions and the addition of two equivalents of SelectfluorTM did not increase the conversion to the mono-fluorinated pyrazoles. Although the fluorination reaction only affords moderate conversion and yield, these results show that the fluorination of pyrazoles is viable and affords some interesting, previously unknown, 3,5-disubstituted-4-fluoropyrazole products. The structure of the novel pyrazole systems were confirmed by x-ray crystallography, where possible, to confirm the presence of the fluorine atom at the 4-position (Figure 26).

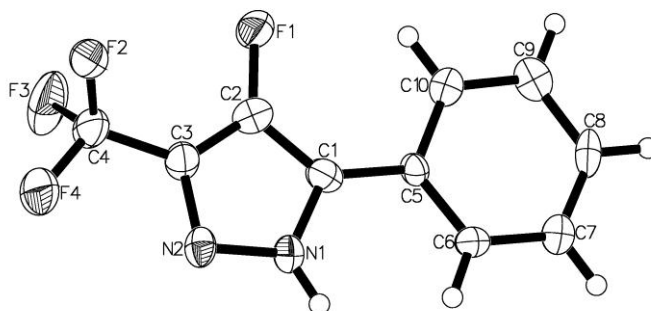
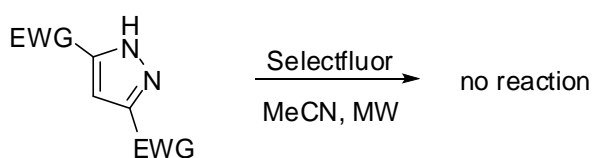


Figure 26: X-ray crystal structure of 4-fluoro-3-phenyl-5-(trifluoromethyl)-1H-pyrazole (**235**)

It is unknown why the reaction does not reach completion, but it is thought that it is due to a competing fluorination reaction between the C-4 carbon and the nitrogen of the pyrazole ring. It was proposed that, on aqueous work-up, the *N*-fluorinated product is converted back to the starting material. A test reaction was carried out where **221** was fluorinated with SelectfluorTM at reflux with ¹⁹F NMR spectroscopy (in d₆-acetonitrile) carried out every hour to see if the formation of the N–F could be observed, but no new signals could be seen between 0 and 40 ppm. Similar to work of Stephens, a small spot could be observed on the bottom of the TLC plate but this product could not be identified although it was assumed by Stephens that this was the N–F pyrazole species.

Similarly, protonation of the pyrazole nitrogen may occur and so the reaction was repeated with addition of a base to see if this could improve the conversion by preventing the formation of a protonated N–H species. The reaction was repeated with 1 equivalent and 0.1 equivalents of sterically hindered base (DIPEA and triethylamine). The reactions were monitored for 5 days at reflux but in both cases no reaction occurred and only starting material could be identified by NMR and mass spectroscopic analysis. The same fluorination reaction was repeated for pyrazole systems where R₁ and R₂ were both electron-withdrawing groups (CF₃, CO₂H, CO₂Me) (Scheme 117). Fluorinations by Selectfluor™ or elemental fluorine, however, gave no observed product and the recovery of unchanged starting materials.



Scheme 117: Fluorination of electron-poor pyrazoles

It can be concluded that the fluorination of deactivated pyrazoles is not possible and that an electron-donating substituent in either the 3 or 5 position of the heterocyclic ring is required to promote the fluorination reaction.

5.3.4 Fluorination of 3,5-Diarylpyrazoles

5.3.4.1 Mono-fluorination of 3,5-Diarylpyrazoles Using Selectfluor

The C–4 fluorination of pyrazoles containing a range of functional groups was successful and so a series of 3,5-diarylpyrazoles were fluorinated to investigate whether substituents on the aromatic ring change the reactivity of the system. Both electron-donating and electron-withdrawing groups were investigated, attached to *ortho*, *meta* and *para* sites, where possible (Table 20).

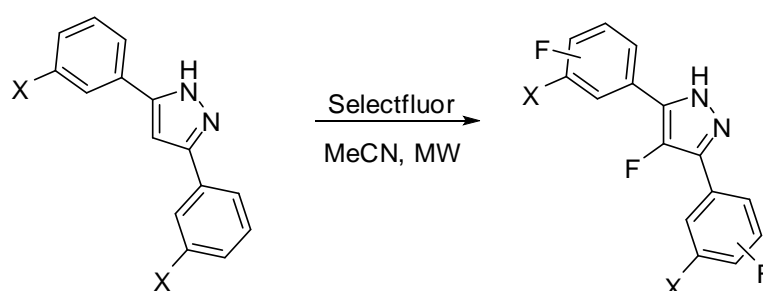
Table 20: Fluorination of 3,5-diarylpyrazoles using Selectfluor™

Pyrazole	4-Fluoropyrazole	Isolated Yield/ %	Pyrazole	4-Fluoropyrazole	Isolated Yield/ %
223		45	230		41 *
224		47	231		10 *
225		31 *	232		12 *
226		41 *	233		45
227		37 *	236		31
228		38 *	237		42
229		36 *			

* GC yield (pure pyrazole product could not be isolated)

The fluorination of 3,5-diaryl substituted pyrazoles proceeded well, in many cases, when Selectfluor™ (1 equiv.) was the fluorinating agent. Again, only ~55 % conversion was obtained. The best results were obtained when R = CF₃ and OMe and in the cases where Cl and Br were in the 4-position of the aromatic ring **246–248**, **242–243**, **238**, **240**). In all reactions the product was very difficult to separate from the starting material, however, the products were isolated pure in most cases, by column chromatography.

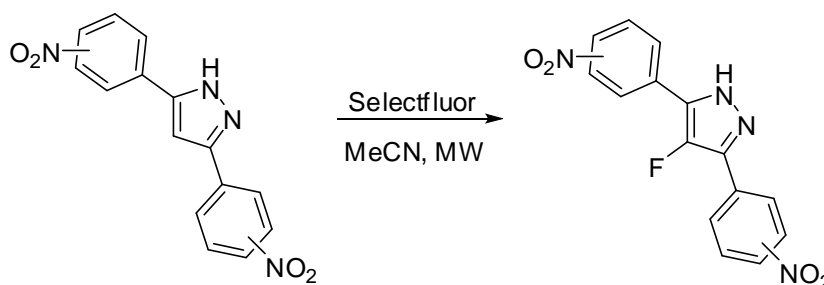
In the cases where bromine and chlorine were in the 3-position of the aromatic ring (**226**, **228**), the reaction gave a complex mixture of products, including products from fluorination on the aromatic ring. This could be seen by signals in the aromatic region (between δ_F -140 and δ_F -160 ppm) of the ^{19}F NMR spectrum. Interestingly, this was not observed when the halogen, X, was in the 4-position.



X = Cl, Br

Scheme 118: Fluorination of 3,5-(3-halogenophenyl)pyrazoles

Fluorination of the **231** and **232** with SelectfluorTM gave very little fluorinated material (10 %), even when the reaction mixture was heated for 1 h at 110 °C (Scheme 119). This could be due to the poor solubility of the starting material or because the aromatic ring is too deactivated to promote the fluorination reaction of the pyrazole ring. This result shows that there is a limit to which substituents can be on the aromatic ring for the fluorination reaction to proceed.

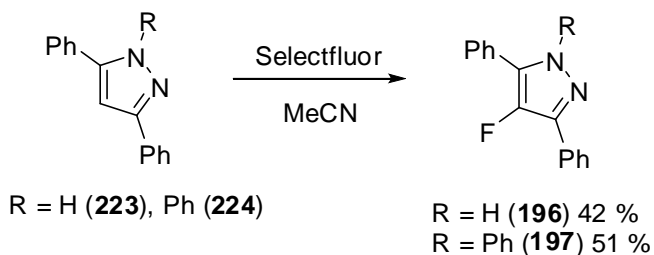


Scheme 119: Fluorination of nitro derivatives

Table 20 shows that the substituent on the ring does not affect the conversion or yield of the reaction, except in the case of the nitro analogue.

5.3.4.2 Mono-fluorination of 3,5-Diarylpyrazoles Using Fluorine

When elemental fluorine in acetic acid was used to fluorinate 3,5-diphenylpyrazoles (**223**, **224**), the mono-fluorinated product could be isolated in comparable yield to when Selectfluor™ was used (Scheme 120).



Scheme 120: Fluorination of pyrazoles using fluorine

When other 3,5-diarylpyrazoles were fluorinated, however, multiple, inseparable fluorinated products were obtained. It was thought that fluorine is too reactive in these cases and promotes fluorination of the aromatic rings as well as on the pyrazole ring. The reaction was carried out in a range of solvents (acetic acid, acetonitrile and formic acid) to see if this improved the selectivity of the reaction, however, the reaction could not be improved and the desired 4-fluoropyrazole could not be separated and isolated.

5.3.4.3 Di-fluorination of 3,5-Diarylpyrazoles using Selectfluor

When two equivalents of Selectfluor™ were used in the fluorination of **223**, an unknown product was obtained, as well as the expected mono-fluorinated product. Instead of the main ^{19}F NMR signal being in the region of δ_{F} -175 ppm for the 4-fluoropyrazole, a singlet was observed at δ_{F} -110 ppm (Figure 27). This was identified as being due to a $-\text{CF}_2$ group and so it was concluded that di-fluorination of the pyrazole had occurred. This product was also proven by mass spectroscopy as $m/z = 256$.

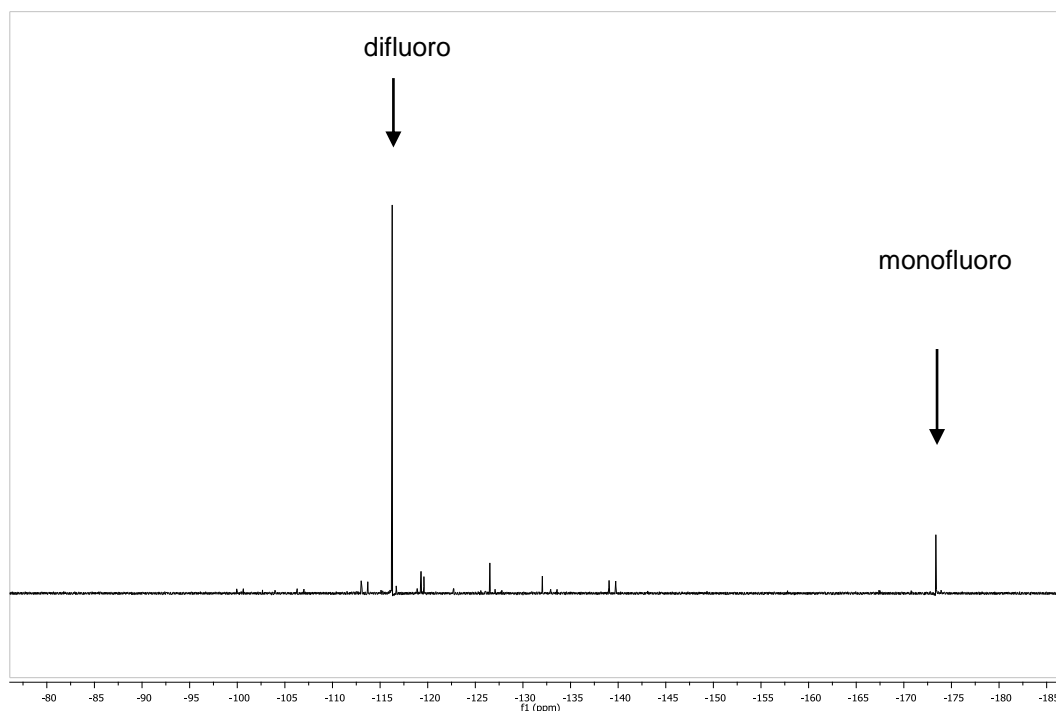
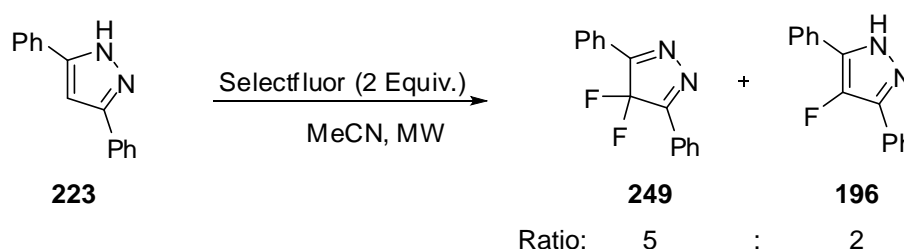


Figure 27: ^{19}F NMR spectrum of the crude mixture


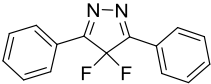
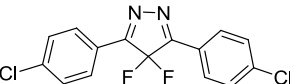
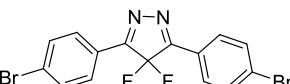
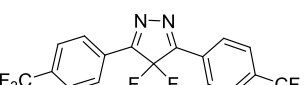
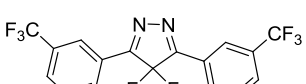
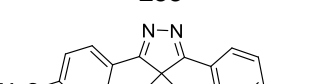
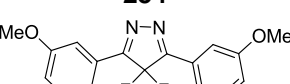
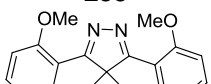
The structure of 4-fluoropyrazole derivative could also be assigned from the ^1H NMR spectrum, which clearly showed the non-equivalence of the two phenyl substituents, with the *ortho* protons of one ring significantly more de-shielded than the other aromatic protons. In contrast, the ^1H NMR spectrum of 4,4-difluoro derivative shows two complex multiplets with an integration ratio of 2:3 for the two equivalent phenyl groups, the four protons in the *ortho* positions appearing at considerably higher chemical shift than the remaining protons.¹¹¹



Scheme 122: Fluorination of 3,5-diphenylpyrazole

The reaction can withstand a range of functional groups on the aryl ring, including electron-donating and electron-withdrawing substituents, in *ortho*, *meta* and *para* positions (Table 21).

Table 21: Di-fluorination of 3,5-diarylpyrroles using Selectfluor™

		
Pyrazole	Difluoropyrazole	Isolated Yield/ %
223	 249	52
225	 250	54
227	 251	54
229	 252	51
230	 253	44
233	 254	45
236	 255	43
237	 256	49

Again, in the case of the 3-chloro- and 3-bromophenyl derivatives (**226**, **228**), multiple products were observed, including those from fluorination on the aromatic ring. The structure of the **254** was proven by X-ray crystallography, where it can easily be seen that there are two fluorine atoms in the 4-position of the pyrazole ring (Figure 28).

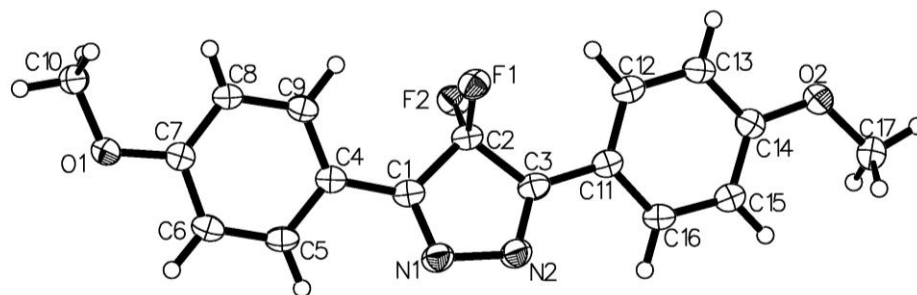
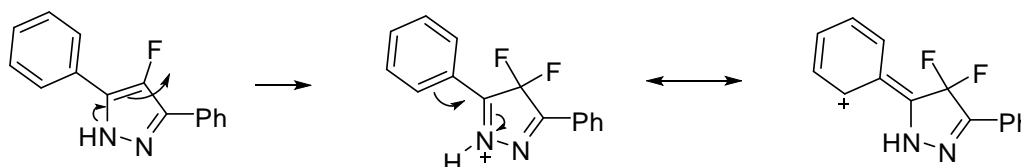


Figure 28: Crystal structure of 4,4-difluoro-3,5-bis(4-methoxyphenyl)-4H-pyrazole (**254**)

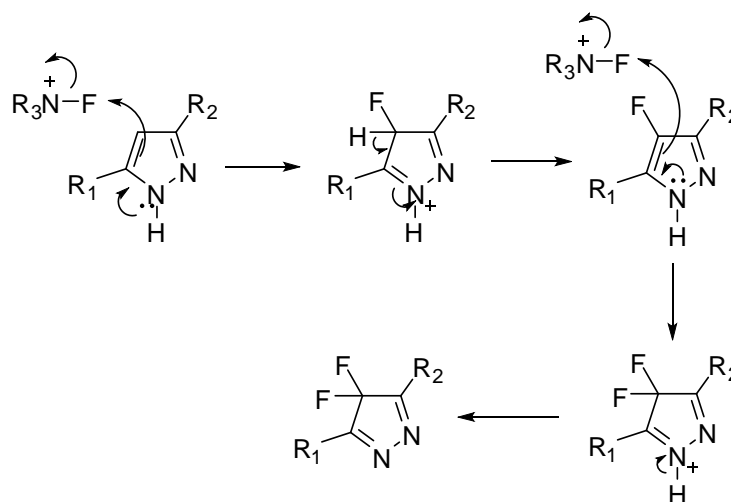
In all reactions a small amount of mono-fluorinated product was observed (~ 10–20 %) and some starting material remained unreacted (30–45 %). However, the di-fluorinated products, in general, elute from the column much more rapidly than the starting material and mono-fluorinated materials and so were more readily isolated. The di-fluorination reaction was attempted with three equivalents of Selectfluor™ but this did not increase the conversion to the di-fluorinated product.

The di-fluorinated product was only observed when 3,5-diarylpyrazoles were fluorinated, and not when R = alkyl or trifluoromethyl groups. It is thought that this is due to the phenyl groups offering extra stabilisation of reaction intermediates (Scheme 123).



Scheme 123: Stabilisation of fluoropyrazoles intermediates

The mechanism of the di-fluorination reaction is thought to involve formation of the mono-fluorinated product through electrophilic attack by one equivalent of the electrophilic fluorine and subsequent attack by the second equivalent of electrophilic fluorine (Scheme 124). The proposed mechanism explains why both mono-fluorinated and di-fluorinated products are observed in the ^{19}F NMR spectrum of the crude product mixtures.



Scheme 124: Mechanism of the di-fluorination of pyrazoles

It was also noted that, after aqueous work up, in some cases, two ^{19}F NMR signals could be seen as an AB system (Figure 29) and this indicated that there may be a by-product containing a chiral centre close to the carbon-fluorine bond which was predicted to be **257**. It was proposed that these signals could be due to hydrolysis of the ring which forms the hydroxy-pyrazoline product.

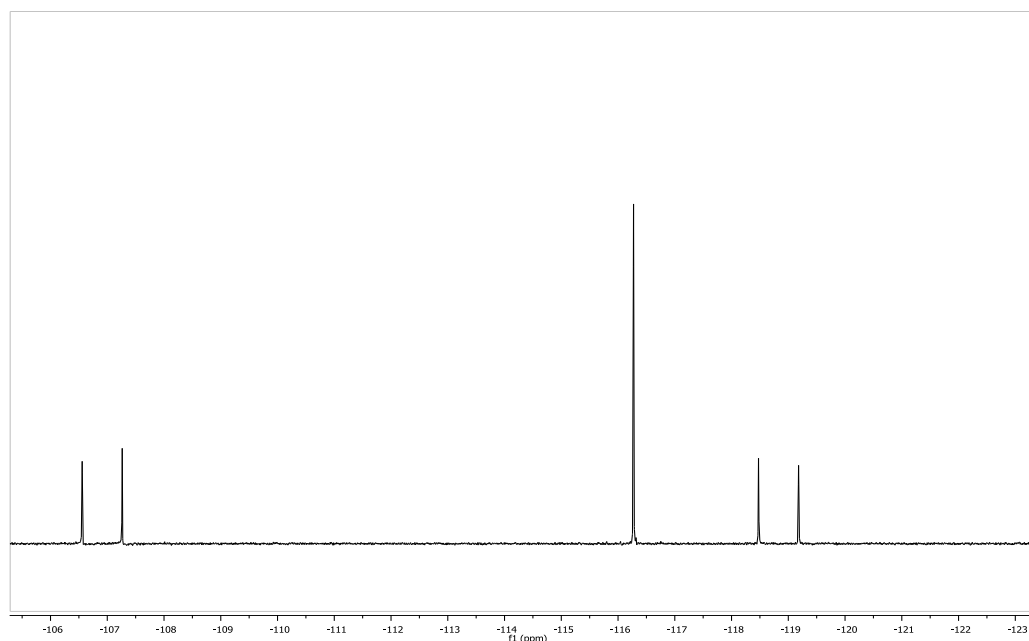
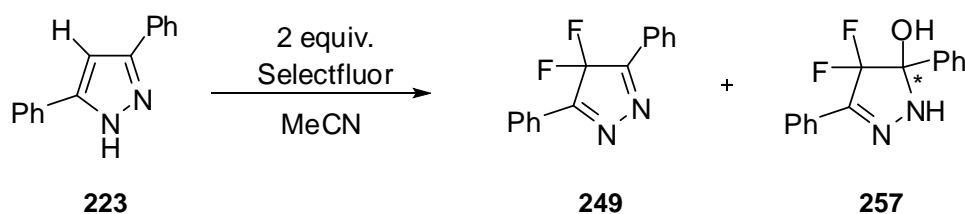


Figure 29: ^{19}F NMR spectrum of hydroxyl by-product

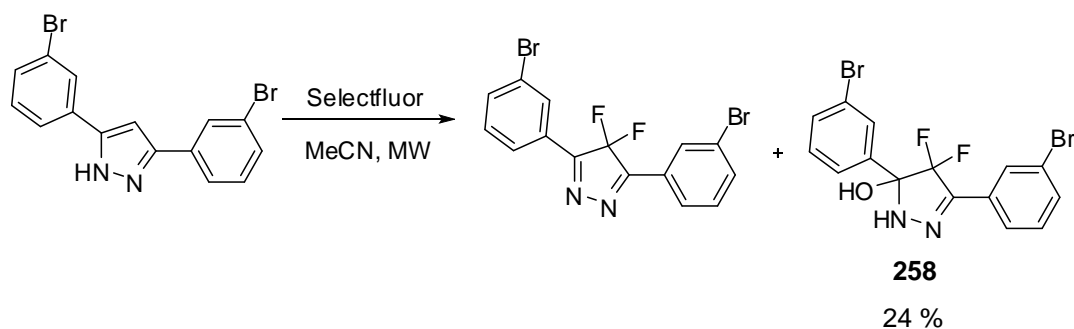
On refluxing the crude product in acid, the ratio of the hydroxy-pyrazoline product was reduced but was not removed completely. It is, however, possible to completely

remove this by-product by recrystallisation. Purification could also be carried out without aqueous work-up to reduce the quantity of the hydroxy-pyrazoline product. The hydroxy-pyrazoline product is an intermediate of the pyrazole formation mechanism and has been seen in other pyrazole syntheses¹¹⁰ including in the reactions to form the pyrazole starting materials, as shown earlier.



Scheme 125: Di-fluorination of 3,5-diphenylpyrazole

The hydroxyl product was thought to be an interesting fluorinated by-product and attempts were made to isolate this. A small amount of the by-product was isolated by column chromatography when the 3-bromophenyl derivative was fluorinated (Scheme 126). This reaction led to a mixture of products, the hydroxyl by-product (**258**) being the only one that could be isolated in low yield.



Scheme 126: Synthesis of the hydroxy-pyrazoline by-product

Figure 30 shows the AB system and shows the large coupling constant. The ¹³C and ¹H NMR spectra also showed that the phenyl rings were no longer equivalent with the ¹H NMR spectrum also showing a broad OH signal clearly.

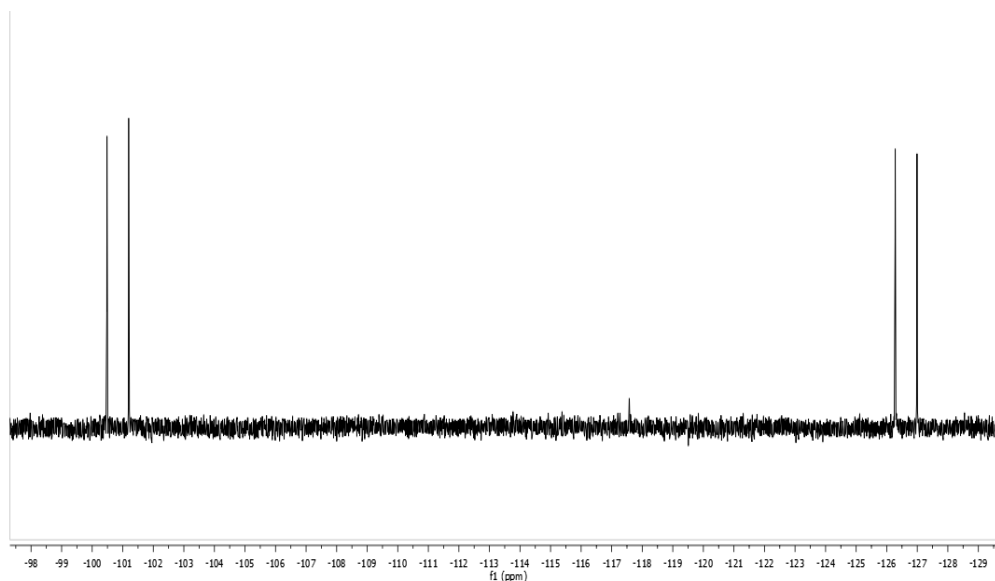
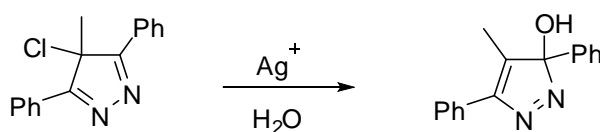


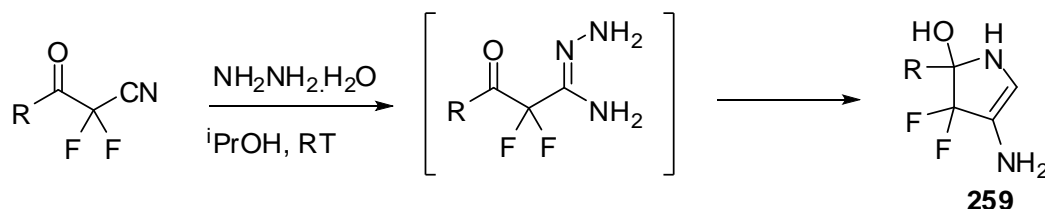
Figure 30: ^{19}F NMR spectrum of the hydroxyl by-product

This hydrolysis reaction has been seen in previous work with halogenated 4H-pyrazoles and has also been formed by silver promoted solvolysis, where the hydroxyl compound, shown in Scheme 127, can be formed.¹¹¹



Scheme 127: Silver promoted solvolysis to afford the hydroxyl-pyrazoline

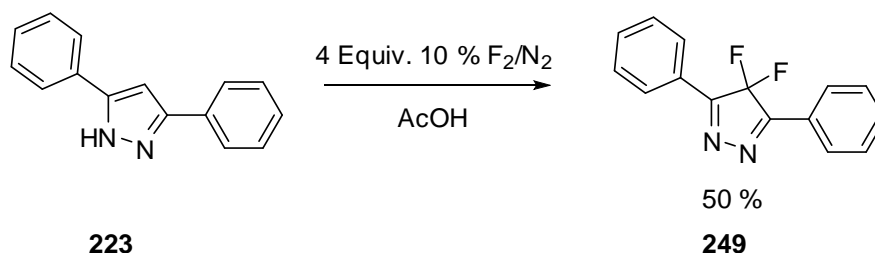
Similarly, evidence for this type of fluorinated hydroxyl-pyrazoline structure, **259**, is also observed in the synthesis of fluorinated pyrazoles, as shown in Scheme 128.⁹⁷



Scheme 128: Evidence for the di-fluoro hydroxy-pyrazoline structure

5.3.4.4 Di-fluorination of 3,5-Diarylpyrazoles Using Fluorine

The di-fluorination of 3,5-diarylpyrazoles with elemental fluorine (4 equiv.) was only successful in the case of **223**, although this proceeded very well with a 50 % isolated yield of the desired di-fluorinated product (Scheme 129).

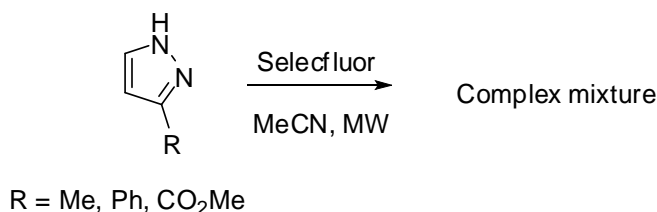


Scheme 129: Di-fluorination of 3,5-diphenylpyrazole using elemental fluorine

Again, when there was a substituent on the phenyl group, the direct fluorination reaction yielded a complex mixture of products which could not be separated due to activation of the aromatic ring by the substituents.

5.3.5 Fluorination of Mono-substituted Pyrazoles

The fluorination reaction was attempted on pyrazoles containing only one substituent but in all cases, multiple fluorination products could be seen in the ¹⁹F NMR spectra. Attempts to separate these products by column chromatography were made, but no pure products could be isolated. The fluorination of 1H-pyrazole was also investigated but this also gave a complex mixture of inseparable products (Scheme 130).



Scheme 130: Fluorination of mono-substituted pyrazoles using Selectfluor

These results show that the fluorination of pyrazoles is only selective when substituents are blocking alternative pyrazole ring sites.

5.4 Conclusions

It has been demonstrated that C-4 fluorination of 3,5-disubstituted pyrazoles is possible when both Selectfluor™ and elemental fluorine are employed as the electrophilic fluorinating agent. The reaction tolerates a range of functional groups but no reaction occurs when both substituents on the pyrazole ring are electron-withdrawing. Although the reaction does not proceed to completion, it is a good indicator that late stage fluorination of pyrazole systems is possible, with very few by-products observed.

It has been shown that a wide variety of 3,5-diarylpyrazoles can be fluorinated successfully to give both mono- and di-fluorinated products, depending on the conditions used. When nitro- substituents are on the phenyl ring, however, the reaction is very slow, leading to only 10 % conversion due to deactivation of the aromatic ring. The fluorination of 3,5-diarylpyrazoles also promotes the formation of the hydroxy-pyrazoline by-products but these can be removed by chromatography and/or recrystallisation.

The first examples of 4,4-difluoro pyrazole derivatives have been isolated and structures proven by x-ray crystallography. These are novel, bench stable fluoro-organic molecules that could be used in the synthesis of more complex structures.

It has also been demonstrated that the fluorination of 1H-pyrazole and monosubstituted pyrazoles gives no selectivity with fluorination occurring at multiple sites and no separation of products being possible.

Chapter 6

Conclusions and Future Work

6.1 Conclusions

The direct fluorination of aromatics has been shown to be ineffective for the synthesis of arylfluorides bearing electron-donating substituents. In most cases conversion from the starting material was poor and multiple fluorinated products were obtained. *Ips*o fluoro-deboronation, however, was demonstrated as a useful tool in the selective synthesis of arylfluorides, particularly in cases where an electron-donating substituent was in the 4-position of the arylboronic acid derivative. Trifluoroborate salts were demonstrated as the superior boronic acid derivatives as these were more reactive and more soluble than their boronic acid and boronate ester analogues. Interestingly, the fluoro-deboronation of heterocyclic systems was also shown to be possible.

Alternatively, the synthesis of 4-fluoropyrazoles was carried out using a range of methods. The step-wise synthesis of 4-fluoropyrazoles was high yielding but requires two synthetic steps and reflux temperatures. On the other hand, the continuous flow two-step process does not require isolation of the 2-fluoro-1,3-diketone and can be carried out in 2 h, with a small amount of solvent. The continuous flow procedure is, however, limited by the steric bulk of the diketone and hydrazine used.

The C-4 fluorination of 3,5-disubstituted pyrazoles was also successful with Selectfluor™ and, in some cases, elemental fluorine, with isolated yields of 40–60 % often obtained. When 3,5-diarylpyrazoles were fluorinated with two equivalents of Selectfluor™, the novel 4,4-difluoropyrazoles could be isolated easily.

6.2 Future Work

6.2.1 Fluoro-deboronation of Aryl and Heterocyclic Boronic Acid Derivatives

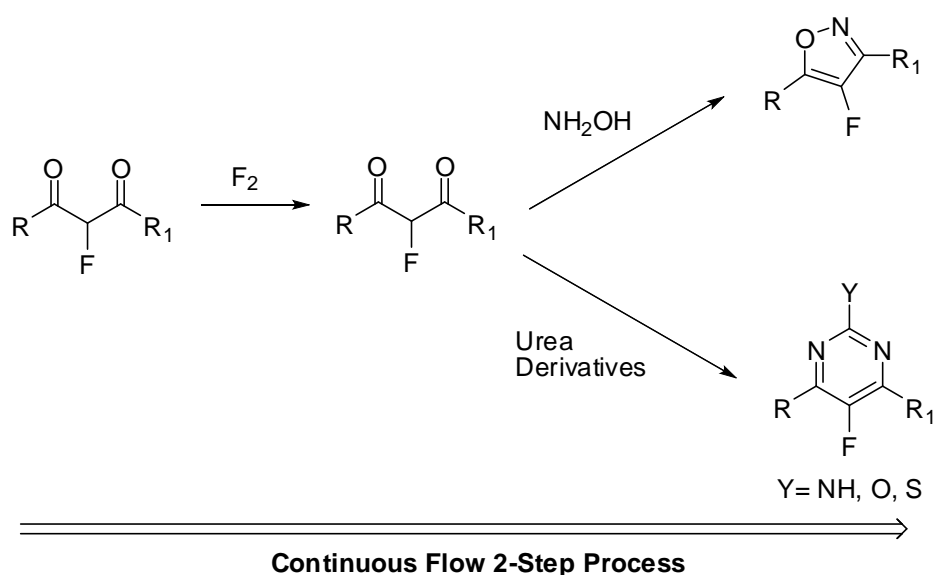
The *ip*so fluoro-deboronation reaction is only possible when an electron-donating substituent is in the 2- or 4-position of the aromatic ring but the fluoro-deboronation of

more complex systems would be beneficial for the pharmaceutical industry. The competing proto-deboronation is the main problem in the fluoro-deboronation reaction and so more research should be carried out to completely understand why and how this occurs and if this can be prevented from taking place. If this is possible, *ipso* fluoro-deboronation could be used as a general method for the synthesis of arylfluorides.

The fluoro-deboronation of heterocyclic boronic acid systems is a particularly interesting result and further research in to this could be of benefit to the life sciences industry. The conversion of the fluoro-deboronation reactions from the starting material was demonstrated to be the main problem with the reaction of hetero-aromatic substrates and so further investigations in to the mechanism must be carried out so that the reaction can be promoted to full conversion, and high yields of the fluoro-heterocyclic products obtained.

6.2.2 Continuous Flow Step-wise Synthesis of Pyrazoles

The step-wise synthesis of fluorinated pyrazoles using the continuous flow set-up gave the desired product in good yield and so it would be interesting to see if this set-up could be used to synthesize alternative fluoro-heterocyclic systems such as fluoro-pyrimidines (using urea derivatives) and fluoro-isoxazoles (using hydroxylamine) in good yield and purity (Scheme 131).



Scheme 131: Continuous flow synthesis of fluoro-heterocycles

6.2.3 Ring Fluorination of Pyrazoles

More research could be carried out to investigate why the fluorination of 3,5-disubstituted pyrazoles does not proceed to full conversion. If full conversion could be achieved then this would allow much simpler purification of the products. Similarly, the fluorination of similar heterocyclic derivatives, such as electron-rich imidazole systems, could also be investigated to see if selective fluorination occurs in a comparable manner.

The pyrazole systems could be interesting substrates to investigate in the photo-physical sciences, with complexation to metals such as iridium being possible (Figure 31).¹¹²

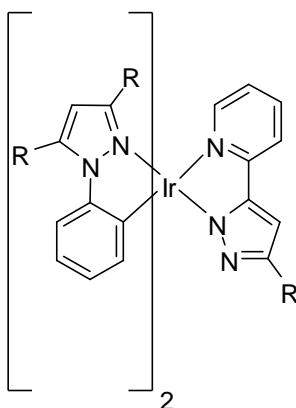
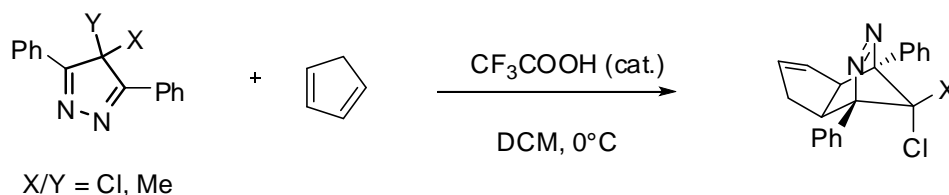


Figure 31: Iridium-pyrazole complex

Alternatively, the [4+2] cycloaddition of 4,4-disubstituted 4H-pyrazoles (as dienes) with alkenes (as dienophiles) is possible due to their reluctance towards tautomerisation to the 2H-pyrazoles (Scheme 132).



Scheme 132: Cyclo-addition reaction to give novel aza-alkane

Much work has concentrated on 4, 4-dialkyl substitution since such 4H-pyrazoles are persistent toward rearrangement and undergo acid-catalysed cycloadditions with

strained (norbornene, norbornadiene, etc.) and electron-rich (cyclopentadiene) alkenes.¹⁰⁷ Halogens as substituents (X, Y = Cl, Br) show a high propensity toward 1,3 migration in pyrazoles, but their 4H form remains due to the labile nature of the N–Cl and N–Br bonds in the corresponding 2H-pyrazoles. The activation by the electron-accepting halogen substituents allows halo-4H-pyrazoles to be suitable diene partners in the Diels-Alder reaction with alkenes.¹¹¹ The chloro- and bromo- derivatives have been shown to be excellent in the Diels-Alder reaction and so it would be interesting to investigate whether the fluorinated analogue would behave in a similar manner to afford some interesting systems.

Experimental Section

7.1 General

NMR Spectroscopy: Proton, carbon and fluorine nuclear magnetic resonance spectra (^1H NMR, ^{13}C NMR and ^{19}F NMR) were recorded on a Varian Inova-500 (^1H NMR, 500 MHz; ^{13}C NMR, 126 MHz; ^{19}F NMR, 470 MHz) or a Varian DD-700 (^1H NMR, 700 MHz; ^{13}C NMR, 176 MHz; ^{19}F NMR, 658 MHz) spectrometer with solvent resonance as the internal standard (^1H NMR, CHCl_3 at 7.26 ppm; ^{13}C NMR, CDCl_3 at 77.36 ppm; ^{19}F NMR, CFCl_3 at 0.00 ppm). ^1H , ^{13}C and ^{19}F spectroscopic data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz), and assignment.

Mass Spectrometry: GC-MS analysis was performed on a Trace GC-MS device (Thermo-Finnigan Corporation) operating in electron impact ionisation (EI^+) mode and accurate mass analysis was achieved with a Xevo QtoF mass spectrometer (Waters Ltd, UK) equipped with an accurate solids analysis probe (ASAP).

Elemental Analysis: C, H and N analyses were collected with an Exeter Analytical CE-440 Elemental Analyser.

IR: Infra-red spectra were recorded on a Perkin Elmer Spectrum RX1 fitted with an ATR attachment.

X-Ray Analysis: All crystallographic data were recorded with a Rigaku R-Axis SPIDER IP diffractometer equipped with Cryostream (Oxford Cryosystems) low temperature device at 120 K with graphite-monochromated MoK α -radiation ($\lambda = 0.71073 \text{ \AA}$).

Melting Point Analysis: Melting points were measured with a Gallenkamp apparatus at atmospheric pressure and are uncorrected.

Microwave: All microwave irradiated reactions were heated in a Biotage InitiatorTM Sixty Microwave using a 0.5–2 mL, 2–5 mL or 10–20 mL microwave vial fitted with a Biotage magnetic follower and sealed with a ResealTM Septum. The microwave was set to heat to a constant temperature, as specified in the relevant experimental procedure, and each reaction was timed from the point at which the target temperature had been reached. After the reaction time had expired, the microwave vial and its contents were cooled to 45 °C by an external flow of nitrogen gas. Reactions involving solvent acetonitrile were heated using the “high” irradiation mode.

Chemicals and Solvents: Unless otherwise stated, commercially available reagents were used without further purification. An Innovative Technology Inc. Solvent Purification System fitted with a Metrohm 831 Karl Fischer Coulometric Titrator was used to dry acetonitrile. Hexane, ethyl acetate and DCM were purchased from Fischer and used without further purification. Flash column chromatography was carried out using Fluorochem Silicagel LC60A (40-63 micron).

7.2 Experimental to Chapter 2

7.2.1 Fluorination of Aromatic Substrates – General Procedure

The substrate (15 mmol) was dissolved in formic acid or acetonitrile (40 mL) in a large glass reaction vessel fitted with a F₂ delivery tube, mechanical stirrer and exhaust tube connected to a scrubber containing soda lime. The apparatus was cooled using a cryo-cooler set to 0 °C and the system was purged with N₂ gas for 10 minutes before F₂ (10 % in N₂) (60 mmol) was allowed to flow into the reaction mixture at the flow-rate controlled by a Brooks InstrumentsTM mass flow controller for 18 h (overnight). Once all fluorine had been used, N₂ was purged through the system for a further 10 minutes. ¹⁹F NMR spectroscopic analysis of the reaction mixture determined if any fluorination had occurred. The product was then washed by water (30 mL) and extracted by DCM (30 mL). The organic extracts were then washed with saturated NaHCO₃ (50 mL) and

dried over MgSO_4 and the solvent removed by vacuum to give a crude product, which was analysed by ^{19}F NMR spectroscopy and GC-MS and purified by either column chromatography or recrystallisation, if required.

Fluorination of 1,2-diethoxybenzene (71)

1,2-Diethoxybenzene (2.49 g, 15.0 mmol), formic acid (40 mL) and F_2 (60 mmol) gave a complex mixture of mono- ($m/z = 184$) and di-fluorinated products ($m/z = 202$) as a yellow/brown oil (1.98 g); ^1H NMR (400 MHz; CDCl_3): δ 1.38–1.49 (m, OCH_2CH_3), 4.01–4.16 (m, OCH_2CH_3), 6.55–6.97 (m, Ar-H); ^{19}F NMR (376 MHz; CDCl_3): δ -121.1, -122.5, -128.0, -130.7, -134.9, -141.1, -146.2, -147.7, -158.2 ppm; m/z (EI^+) 166, 184, 202; No further purification was attempted. (Lit.¹¹³: 1,2-diethoxy-4-fluorobenzene: δ_{F} -130.5 ppm).

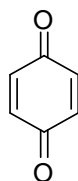
Fluorination of 1,3-dimethoxybenzene (32)

1,3-Dimethoxybenzene (2.04 g, 15.0 mmol), formic acid (40 mL) and F_2 (60 mmol) gave mono- ($m/z = 156$), di- ($m/z = 174$) and tri-fluorinated ($m/z = 192$) products as a yellow oil (1.12 g); ^1H NMR (400 MHz; CDCl_3): δ 3.82–4.09 (m, OCH_3), 6.51–6.71 (m, Ar-H); ^{19}F NMR (376 MHz; CDCl_3): δ -123.2, -135.3, -139.3, -142.0, -143.5, -146.5, -152.8, -159.1, 162.0; m/z (EI^+) 156, 174, 192; No further purification was attempted. (Lit.⁶⁶: 1-fluoro-2,4-dimethoxybenzene: δ_{F} -146.5 ppm, lit.⁶⁷: 2-fluoro-1,3-dimethoxybenzene: δ_{F} -159.1 ppm, lit.⁶⁶: 1,5-difluoro-2,4-dimethoxybenzene: δ_{F} -142.0 ppm, lit.⁶⁶: 1,2,4-trifluoro-3,5-dimethoxybenzene: δ_{F} -141.2, -156.7 and -163.4 ppm).

Fluorination of 1,3-Diethoxybenzene (77)

1,3-Diethoxybenzene (2.49 g, 15.0 mmol), in formic acid (40 mL) and F_2 (60 mmol) gave mono- ($m/z = 184$), di- ($m/z = 202$) and tri-fluorinated ($m/z = 220$) products as a yellow oil (1.69 g); ^1H NMR (400 MHz; CDCl_3): δ 1.40–1.55 (m, OCH_2CH_3), 3.97–4.25 (m, OCH_2CH_3), 6.24–6.97 (m, Ar-H); ^{19}F NMR (376 MHz; CDCl_3): δ -101.4, -123.1, -133.5, -138.2, -140.7, -142.9, -148.6, -157.6 ppm; m/z (EI^+) 166, 184, 202, 220; No further purification was attempted.

1,4-Benzoquinone (**80**)



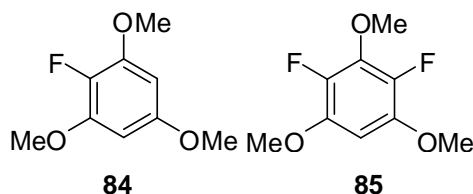
1,4-Dimethoxybenzene (2.04 g, 15.0 mmol), formic acid (40 mL) and F₂ (60 mmol) after column chromatography over silica gel using 7:3 hexane/ethyl acetate as the eluent, gave *1,4-benzoquinone* (0.703 g, 43 %) as a yellow solid which turned brown after long term exposure to light; m.p. 115–117 °C [lit.⁴ 115 °C]; (Found: [MH]⁺, 109.0316. C₆H₄O₂ requires: [MH]⁺, 109.0290); (Found: C, 66.7; H, 4.0, C₆H₄O₂ requires: C, 66.7; H, 3.7 %); IR: 1652 cm⁻¹ (ν_{C=O}), 3250 cm⁻¹ (ν_{OH}); ¹H NMR (400 MHz; CDCl₃): δ 6.81 (s, 4H, CH); ¹³C NMR (126 MHz; CDCl₃): δ 138.1 (2-C), 188.5 (1-C); *m/z* (EI⁺) 108.1 ([M]⁺, 100 %), 82.2 (43), 80.1 (34), 54.4 (98). All data was consistent with the literature⁵.

7.2.2 Direct Fluorination of Aromatics Using the Flow Reactor - General Procedure

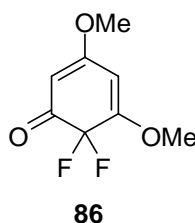
After purging the continuous flow apparatus with nitrogen, fluorine, as a 10 % mixture in nitrogen (v:v), was passed through the microreactor via an inlet port at a prescribed flow rate (15 mL/ min) that was controlled by a Brooks Instruments™ mass flow controller. The microreactor was cooled by an external cryostat to 5–10 °C. The substrate mixture was injected by a mechanised syringe pump into the microreactor channel at a prescribed flow-rate (1.5 mL/ min) through the substrate inlet port. After passing through the microreactor and outlet port, excess fluorine gas and volatile waste products were passed through a scrubber filled with soda lime. Products were collected in a PTFE collection vessel and ¹⁹F NMR spectroscopic analysis of the reaction mixture determined if any fluorination had occurred. The product was then washed by water (30 mL) and extracted by DCM (3 x 30 mL). The organic extracts were then washed with saturated NaHCO₃ (50 mL), dried over MgSO₄ and the solvent removed by vacuum to give a crude product, which was analysed by ¹⁹F NMR spectroscopy and GC-MS and purified by either column chromatography or recrystallisation, if required.

Fluorination of 1,3,5-trimethoxybenzene (82)

1,3,5-Trimethoxybenzene (0.50 g, 2.97 mmol), formic acid (5 mL) and F₂, after purification by column chromatography with DCM as the eluent, gave 2-fluoro-1,3,5-trimethoxybenzene and 2,4-difluoro-1,3,5-trimethoxybenzene in a 7:1 mixture as a yellow oil (0.12 g), 6,6-difluoro-3,5-dimethoxycyclohexa-2,4-dienone (0.15 g, 27 %) as pale yellow crystals and 4,4-difluoro-3,5-dimethoxycyclohexa-2,5-dienone (0.17 g, 30 %) as white crystals.

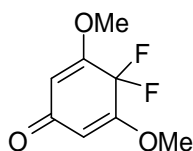


Mixture (7:1) consisted of 2-fluoro-1,3,5-trimethoxybenzene (**84**); ¹H NMR (400 MHz; CDCl₃): δ 3.96 (9H, s, OCH₃), 6.15 (2H, d, ¹J_{HF} 6.2, 4-H); ¹³C NMR (176 MHz; CDCl₃) δ 55.3 (OCH₃), 55.6 (OCH₃), 92.9 (4-C), 137.7 (d, ¹J_{CF} 236.0, 2-C), 148.6 (d, ²J_{CF} 9.2, 3-C), 161.5 (5-C); ¹⁹F NMR (376 MHz; CDCl₃): δ -168.6 (t ⁴J_{HF} 6.2); *m/z* (EI⁺) 186.1 ([M]⁺, 100 %), 157.3 (40), 143.0 (32), 128.4 (12), 69.0 (12); and 2,4-difluoro-1,3,5-trimethoxybenzene (**85**); ¹H NMR (400 MHz; CDCl₃): δ 3.76, (6H, s, OCH₃), 3.77 (3H, s, OCH₃), 6.09 (1H, s, 6-H); ¹³C NMR (176 MHz; CDCl₃) δ 56.5 (OCH₃), 57.1 (OCH₃), 92.3 (6-C), 140.6 (dm, ¹J_{CF} 238.0, 2-C, 4-C), 143.8 (dd, ²J_{CF} 10.0, ³J_{CF} 3.4, 3-C), 155.5 (d, ²J_{CF} 3.0, 5-C); ¹⁹F NMR (376 MHz; CDCl₃): δ -160.5 (d ⁴J_{HF} 7.6); *m/z* (EI⁺) 204.0 ([M]⁺, 100 %), 161.2 (52), 146.0 (22), 115.1 (10).



6,6-difluoro-3,5-dimethoxycyclohexa-2,4-dienone (**86**) m.p. 104–106 °C [lit.¹¹⁶ 105–107 °C]; (Found: [MH]⁺, 191.0515. C₈H₈F₂O₃ requires: [MH]⁺, 191.0520); IR: 1701 cm⁻¹ (ν_{C=O}); ¹H NMR (400 MHz; CDCl₃): δ 3.82 (3H, s, OCH₃), 3.84 (3H, s, OCH₃), 5.29 (1H, q, ⁴J_{HF} 1.9, 2-H), 5.33 (1H, q, ⁴J_{HF} 2.3, 4-H); ¹³C NMR (176 MHz;

CDCl₃) δ 56.6 (OCH₃), 56.9 (OCH₃), 92.9 (t, $^3J_{CF}$ 2.1, 4-C), 97.5 (t, $^3J_{CF}$ 5.0, 2-C), 101.7 (t, $^1J_{CF}$ 247.4, 6-C), 158.3 (t, $^2J_{CF}$ 22.0, 5-C), 173.3 (3-C), 184.4 (t, $^2J_{CF}$ 22.6, 1-C); ^{19}F NMR (376 MHz; CDCl₃): δ -113.4 (t, $^4J_{HF}$ 2.2); m/z (EI⁺) 190.1 ([M]⁺, 100 %), 162.9 (78), 147.3 (83), 132.3 (52), 104.1 (30), 69.4 (38).



83

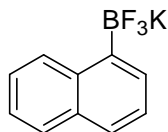
4,4-difluoro-3,5-dimethoxycyclohexa-2,5-dienone (83) m.p. 143–145 °C [lit.³⁰ 140–143 °C]; (Found [MH]⁺ 191.0528 C₈H₈F₂O₃ requires: [MH]⁺ 191.0442); IR: 1698 cm⁻¹ ($\nu_{C=O}$); ^1H NMR (400 MHz; CDCl₃): δ 3.77 (6H, s, OCH₃), 5.43 (1H, t, $^4J_{HF}$ 2.4, 2-H); ^{13}C NMR (176 MHz; CDCl₃) δ 56.7 OCH₃), 102.4 (t, $^4J_{CF}$ 3.6, 2-C), 106.4 (t, $^1J_{CF}$ 242.8, 4-C), 161.0 (t, $^2J_{CF}$ 22.1, 3-C), 184.5 (1-C); ^{19}F NMR (376 MHz; CDCl₃): δ -112.5 (t, $^4J_{HF}$ 2.2); m/z (EI⁺) 190.1 ([M]⁺, 100 %), 147.4 (64), 119.5 (20), 104.0 (30), 69.6 (22).

7.3 Experimental to Chapter 3

7.3.1 Synthesis of Potassium Trifluoroborate Salts from Boronic Acids – General Procedure

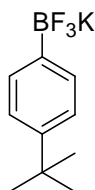
A saturated aqueous solution of KHF₂ was added drop-wise to a concentrated solution of the boronic acid in methanol or acetone at room temperature and was stirred for 30 min. A white precipitate formed and the solvents were evaporated to dryness to give a white solid. Hot acetone was added to the mixture and any solids filtered. The filtrate was then evaporated to dryness and this process was repeated at least twice to give the desired trifluoroborate. GC and NMR spectroscopy were used to check the boronic acid reaction conversion.

*Potassium trifluoro(naphthalen-1-yl)borate (95)*⁷¹



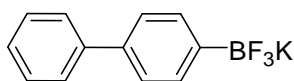
Saturated aqueous KHF_2 (3.75 g, 48.0 mmol), naphthalen-1-ylboronic acid (2.50 g, 14.5 mmol) and methanol gave *potassium trifluoro(naphthalen-1-yl)borate* (2.97 g, 88 %) as a white powder; m.p. 219–220 °C [lit. 221 °C]; ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{CO}$): δ 7.31–7.20 (3H, m, Ar-H), 7.56 (1H, d, $^3J_{\text{HH}}$ 8.1, Ar-H), 7.68 (2H, dd, $^3J_{\text{HH}}$ 6.5, $^4J_{\text{HH}}$ 2.8, Ar-H), 8.58 (1H, dm, $^3J_{\text{HH}}$ 8.8, Ar-H); ^{13}C NMR (176 MHz; $(\text{CD}_3)_2\text{CO}$): δ 123.1, 123.6 (Ar), 124.9 (Ar), 125.3 (Ar), 127.3 (Ar), 128.8 (Ar), 130.8 (Ar), 133.6 (Ar), 137.4 (Ar); ^{11}B NMR (225 MHz; $(\text{CD}_3)_2\text{CO}$) δ 3.89 (q, $^1J_{\text{BF}}$ 55.1); ^{19}F NMR (658 MHz, $(\text{CD}_3)_2\text{CO}$): δ -138.6 (m); m/z (ASAP⁺) 176.1 ($[\text{M} - \text{KF}]^+$).

*Potassium (4-tert-butylphenyl)trifluoroborate (97)*¹¹⁷



Saturated aqueous KHF_2 (3.62 g, 46.3 mmol), 4-*tert*-butylphenylboronic acid (2.50 g, 14.0 mmol) and methanol gave *potassium (4-tert-butylphenyl)trifluoroborate* (3.01 g, 90 %) as white crystals; m.p. > 200 °C; ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{CO}$): δ 1.26 (9H, s, CH_3), 7.14 (2H, d $^3J_{\text{HH}}$ 7.9, 3-*H*), 7.40 (2H, d, $^3J_{\text{HH}}$ 7.8, 2-*H*); ^{13}C NMR (176 MHz; $(\text{CD}_3)_2\text{CO}$): δ 31.0 ($\text{C}(\text{CH}_3)_3$), 33.7 ($\text{C}(\text{CH}_3)_3$), 122.8 (3-*C*), 131.4 (2-*C*), 147.0 (4-*C*); ^{11}B NMR (225 MHz; $(\text{CD}_3)_2\text{CO}$): δ 3.67 (m); ^{19}F NMR (658 MHz, $(\text{CD}_3)_2\text{CO}$) δ -141.9 (m); m/z (ASAP⁺) 182.1 ($[\text{M} - \text{KF}]^+$).

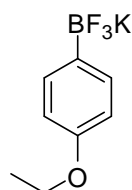
*Potassium biphenyl-4-yltrifluoroborate (99)*¹¹⁸



Saturated aqueous KHF_2 (3.25 g, 41.7 mmol), biphenyl-4-ylboronic acid (2.50 g, 12.6 mmol) and methanol gave *potassium biphenyl-4-yltrifluoroborate* (2.98 g, 91 %) as

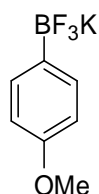
white crystals; m.p. > 270 °C; ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{CO}$): δ 7.24 (1H, tt, $^3J_{\text{HH}}$ 7.4, $^4J_{\text{HH}}$ 1.2, 4'-H), 7.37–7.40 (4H, m, Ar-H), 7.55–7.61 (4H, m, Ar-H); ^{13}C NMR (176 MHz; $(\text{CD}_3)_2\text{CO}$): δ 124.5 (Ar), 126.5 (Ar), 128.5 (Ar), 132.2 (Ar), 137.3 (Ar), 142.5 (Ar); ^{11}B NMR (225 MHz; $(\text{CD}_3)_2\text{CO}$): δ 3.38 (m); ^{19}F NMR (658 MHz, $(\text{CD}_3)_2\text{CO}$): δ -142.7 (m); m/z (ASAP $^+$) 202.1 ($[\text{M} - \text{KF}]^+$).

Potassium (4-ethoxyphenyl)trifluoroborate (104)



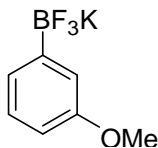
Saturated aqueous KHF_2 (3.88 g, 49.7 mmol), 4-ethoxyphenylboronic acid (2.50 g, 15.1 mmol) and methanol gave *potassium (4-ethoxyphenyl)trifluoroborate* (3.10 g, 90 %) as white crystals; m.p. > 200 °C; ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{CO}$): δ 1.29 (3H, t, $^3J_{\text{HH}}$ 7.0, CH_2CH_3), 3.94 (2H, q, $^3J_{\text{HH}}$ 7.0, CH_2CH_3), 6.65 (2H, d, $^3J_{\text{HH}}$ 7.9, 3-H), 7.35 (2H, d, $^3J_{\text{HH}}$ 8.2, 2-H); ^{13}C NMR (176 MHz; $(\text{CD}_3)_2\text{CO}$): δ 14.3 (CH_2CH_3), 62.4 (CH_2CH_3), 112.4 (3-C), 132.2 (2-C), 157.1 (4-C); ^{11}B NMR (225 MHz; $(\text{CD}_3)_2\text{CO}$): δ 3.63 (m); ^{19}F NMR (658 MHz, $(\text{CD}_3)_2\text{CO}$): δ -141.5 (m); m/z (ASAP $^+$) 170.1 ($[\text{M} - \text{KF}]^+$).

*Potassium trifluoro(4-methoxyphenyl)borate (106)*⁷¹



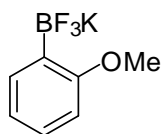
Saturated aqueous KHF_2 (3.39 g, 43.4 mmol), 4-methoxyphenylboronic acid (2.00 g, 13.2 mmol) and methanol gave *potassium trifluoro(4-methoxyphenyl) borate* (2.61 g, 92 %) as white crystals; m.p. > 260 °C; ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{CO}$): δ 3.81 (3H, s, OMe), 6.68 (2H, d, $^3J_{\text{HH}}$ 8.3, 3-H), 7.38 (2H, d, $^3J_{\text{HH}}$ 8.3, 2-H); ^{13}C NMR (176 MHz; $(\text{CD}_3)_2\text{CO}$): δ 54.3 (OMe), 112.4 (2-C), 132.8 (3-C), 157.9 (4-C); ^{11}B NMR (225 MHz; $(\text{CD}_3)_2\text{CO}$): δ 3.59 (m); ^{19}F NMR (658 MHz, $(\text{CD}_3)_2\text{CO}$): δ -141.9 (m); m/z (ES $^-$) 175.1 ($[\text{M} - \text{K}]^+$).

Potassium trifluoro(3-methoxyphenyl)borate (108)



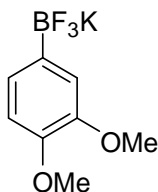
Saturated aqueous KHF_2 (3.39 g, 43.4 mmol), 3-methoxyphenylboronic acid (2.00 g, 13.2 mmol) and methanol gave *potassium trifluoro(3-methoxyphenyl) borate* (2.40 g, 85 %) as white crystals; m.p. > 250 °C; ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{CO}$): δ 3.70 (3H, s, OMe), 7.58 (1H, ddd, $^3J_{\text{HH}}$ 8.0, $^4J_{\text{HH}}$ 2.6, 1.0, 4-*H*), 7.00 (1H, t, $^3J_{\text{HH}}$ 11.7, 5-*H*), 7.04–7.06 (2H, m, Ar-*H*); ^{13}C NMR (176 MHz; $(\text{CD}_3)_2\text{CO}$): δ 54.0 (OMe), 110.6 (4-*C*), 116.7 (2-*C*), 124.9 (6-*C*), 127.0 (5-*C*), 158.8 (3-*C*); ^{11}B NMR (225 MHz; $(\text{CD}_3)_2\text{CO}$): δ 3.89 (m); ^{19}F NMR (658 MHz, $(\text{CD}_3)_2\text{CO}$): δ -142.9 (m); m/z (ES^-) 175.1 ($[\text{M} - \text{K}]^+$).

Potassium trifluoro(2-methoxyphenyl)borate (110)



Saturated aqueous KHF_2 (3.39 g, 43.4 mmol), 2-methoxyphenylboronic acid (2.00 g, 13.2 mmol) and methanol gave *potassium trifluoro(2-methoxyphenyl) borate* (2.53 g, 90 %) as white crystals; m.p. > 250 °C; ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{CO}$): δ 3.75 (3H, s, OMe), 6.76 (2H, m, Ar-*H*), 7.05 (1H, td, $^3J_{\text{HH}}$ 7.4, $^4J_{\text{HH}}$ 1.7, 4-*H*), 7.50 (1H, d, $^3J_{\text{HH}}$ 7.4, 6-*H*); ^{13}C NMR (176 MHz; $(\text{CD}_3)_2\text{CO}$): δ 54.3 (OMe), 109.9 (3-*C*), 119.4 (6-*C*), 126.7 (5-*C*), 133.8 (4-*C*), 163.0 (2-*C*); ^{11}B NMR (225 MHz; $(\text{CD}_3)_2\text{CO}$): δ 3.98 (m); ^{19}F NMR (658 MHz, $(\text{CD}_3)_2\text{CO}$): δ -140.9 (m); m/z (ES^-) 175.1 ($[\text{M} - \text{K}]^+$).

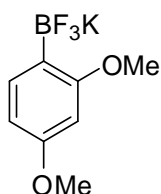
Potassium (3,4-dimethoxyphenyl)trifluoroborate (119)



Saturated aqueous KHF_2 (2.83 g, 36.3 mmol), 3,4-dimethoxyphenylboronic acid (2.00 g, 11.0 mmol) and acetone gave *potassium trifluoro(3,4-dimethoxyphenyl) borate* (1.87

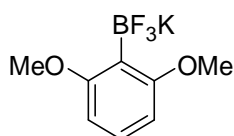
g, 70 %) as white crystals; m.p. > 250 °C; ^1H NMR (700 MHz, D_2O): δ 3.70 (6H, s, OMe), 6.56–6.62 (1H, m, 2-*H*), 6.99–7.02 (2H, m, Ar-H); ^{13}C NMR (176 MHz; D_2O): δ 55.4 (OMe), 55.6 (OMe), 111.8 (2-C), 114.4 (5-C), 124.0 (6-C), 147.3 (3-C), 147.3 (4-C); ^{11}B NMR (225 MHz; $(\text{CD}_3)_2\text{CO}$): δ 1.03 (m); ^{19}F NMR (658 MHz, D_2O): δ 143.7 (m); m/z (ES^-) 205.1 ($[\text{M} - \text{K}]^+$).

Potassium trifluoro(2,4-dimethoxyphenyl)borate (123)



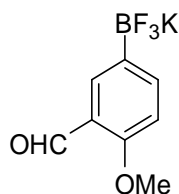
Saturated aqueous KHF_2 (2.83 g, 36.3 mmol), 2, 4-dimethoxyphenylboronic acid (2.00 g, 11.0 mmol) and acetone gave *potassium trifluoro(2, 4-dimethoxyphenyl)borate* (1.97 g, 73 %) as white crystals; m.p. > 250 °C; ^1H NMR (700 MHz, D_2O): δ 3.76 (6H, s, OCH_3), 6.95 (1H, d, $^3J_{\text{HH}}$ 8.3, 3-*H*), 7.65 (1H, d, $^3J_{\text{HH}}$ 8.3, 2-*H*), 7.71 (1H, s, 6-*H*), 9.98 (1H, s, CHO); ^{13}C NMR (176 MHz; D_2O): δ 55.7 (OCH_3), 111.9 (3-C), 123.2 (5-C), 134.2 (6-C), 140.1 (2-C), 161.1 (4-C), 194; ^{11}B NMR (225 MHz; $(\text{CD}_3)_2\text{CO}$): δ 0.98 (m); ^{19}F NMR (658 MHz, D_2O): δ .142.9 (m); m/z (ES^-) 203.1 ($[\text{M} - \text{K}]^+$).

Potassium trifluoro(2,6-dimethoxyphenyl)borate (127)



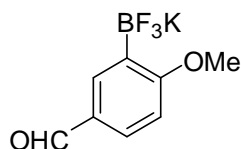
Saturated aqueous KHF_2 (2.83 g, 36.3 mmol), 2, 4-dimethoxyphenylboronic acid (2.00 g, 11.0 mmol) and acetone gave *potassium trifluoro(2,4-dimethoxyphenyl)borate* (1.89 g, 70 %) as white crystals; m.p. > 250 °C; ^1H NMR (700 MHz, D_2O): δ 6.72 (1H, d, $^3J_{\text{HH}}$ 8.4, 3-*H*, 5-*H*), 7.39 (1H, t, $^3J_{\text{HH}}$ 8.4, 4-*H*); ^{13}C NMR (176 MHz; D_2O): δ 55.9 (OMe), 104.9 (3-C), 130.2 (4-C), 163.4 (2-C); ^{11}B NMR (225 MHz; $(\text{CD}_3)_2\text{CO}$): δ 1.01 (m); ^{19}F NMR (658 MHz, D_2O): δ -142.9 (m); m/z (ES^-) 203.1 ($[\text{M} - \text{K}]^+$).

Potassium trifluoro(3-formyl-4-methoxyphenyl)borate (131)



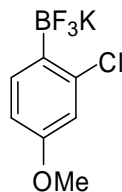
Saturated aqueous KHF_2 (2.87 g, 36.7 mmol), 3-formyl-4-methoxyphenylboronic acid (2.00 g, 11.1 mmol) and gave *potassium trifluoro(3-formyl-4-methoxyphenyl)borate (X)* (1.77 g, 66 %) as white crystals; m.p. > 250 °C; ^1H NMR (700 MHz, D_2O): δ 3.76 (6H, s, OCH_3), 6.95 (1H, d, $^3J_{\text{HH}}$ 8.3, 5-*H*), 7.65 (1H, d, $^3J_{\text{HH}}$ 8.3, 6-*H*), 7.71 (1H, s, 2-*H*), 9.98 (1H, s, CHO); ^{13}C NMR (176 MHz; D_2O): δ 56.1 (OCH_3), 111.9 (5-*C*), 123.2 (3-*C*), 134.2 (6-*C*), 140.1 (2-*C*), 161.1 (4-*C*), 194.8 (CHO); ^{11}B NMR (225 MHz; $(\text{CD}_3)_2\text{CO}$): δ 4.01 (m); ^{19}F NMR (658 MHz, D_2O): δ -142.9 (m); m/z (ES^-) 203.1 ($[\text{M} - \text{K}]^+$).

Potassium trifluoro(5-formyl-2-methoxyphenyl)borate (133)



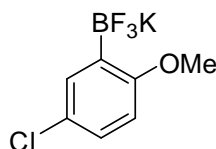
Saturated aqueous KHF_2 (2.87 g, 36.7 mmol), 5-formyl-2-methoxyphenylboronic acid (2.00 g, 11.1 mmol) and acetone gave *potassium trifluoro(5-formyl-2-methoxyphenyl)borate* (1.86 g, 69 %) as white crystals; ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{CO}$): δ 3.84 (3H, s, OMe), 6.92 (1H, d, $^3J_{\text{HH}}$ 8.4, 3-*H*), 7.65 (1H, dd, $^3J_{\text{HH}}$ 8.4, $^4J_{\text{HH}}$ 2.4, 4-*H*), 8.04 (1H, s, 6-*H*), 9.83 (1H, s, CHO); ^{13}C NMR (176 MHz; $(\text{CD}_3)_2\text{CO}$): δ 54.7 (OCH_3), 114.9 (3-*C*), 129.2 (5-*C*), 129.4 (4-*C*), 136.2 (6-*C*), 168.1 (2-*C*), 191.1 (CHO); ^{11}B NMR (225 MHz; $(\text{CD}_3)_2\text{CO}$): δ 2.78 (m); ^{19}F NMR (658 MHz, $(\text{CD}_3)_2\text{CO}$): δ -141.6 (m); m/z (ES^-) 203.2 ($[\text{M} - \text{K}]^+$).

Potassium (2-chloro-4-methoxyphenyl)trifluoroborate (135)



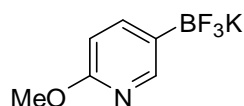
Saturated aqueous KHF_2 (4.16 g 53.1 mmol), 2-chloro-4-methoxyphenylboronic acid (3.0 g, 16.1 mmol) and acetone gave *potassium (2-chloro-4-methoxyphenyl)trifluoroborate* (2.95 g, 74 %) as white crystals; m.p. > 250 °C; ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{CO}$): δ 3.78 (3H, s, OMe), 6.83 (1H, d, $^3J_{\text{HH}}$ 8.0, 5-*H*), 7.32 (1H, d, $^3J_{\text{HH}}$ 7.9, 6-*H*), 7.40 (1H, s, 3-*H*); ^{13}C NMR (176 MHz; $(\text{CD}_3)_2\text{CO}$): δ 55.2 (OCH₃), 111.2 (5-*C*), 120.2 (3-*C*), 131.0 (2-*C*), 133.1 (6-*C*), 152.8 (4-*C*); ^{11}B NMR (225 MHz; $(\text{CD}_3)_2\text{CO}$): δ 3.14 (m); ^{19}F NMR (658 MHz, $(\text{CD}_3)_2\text{CO}$): δ -142.4 (m); m/z (ASAP⁺) 190.1 ([M - KF]⁺).

Potassium trifluoro(2-methoxy-5-chlorophenyl)borate (137)



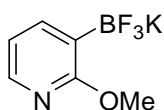
Saturated aqueous KHF_2 (4.16 g 53.1 mmol), 2-methoxy-5-chlorophenylboronic acid (3.0 g, 16.1 mmol) and acetone gave *potassium trifluoro(2-methoxy-5-chlorophenyl)borate* (3.06 g, 76 %) as white crystals; m.p. > 250 °C; ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{CO}$): δ 3.82 (3H, s, OMe), 6.86 (1H, d, $^3J_{\text{HH}}$ 8.0, 3-*H*), 7.35 (d, $^3J_{\text{HH}}$ 7.8, 4-*H*), 7.43 (1H, s, 6-*H*); ^{13}C NMR (176 MHz; $(\text{CD}_3)_2\text{CO}$): δ 55.7, (OCH₃), 111.7 (3-*C*), 120.5 (5-*C*), 131.3 (6-*C*), 133.4 (4-*C*), 153.2 (2-*C*); ^{11}B NMR (225 MHz; $(\text{CD}_3)_2\text{CO}$): δ 3.09 (m); ^{19}F NMR (658 MHz, $(\text{CD}_3)_2\text{CO}$): δ -142.4 (m); m/z (ASAP⁺) 190.2 ([M - KF]⁺).

Potassium trifluoro(6-methoxypyridin-3-yl)borate (145)



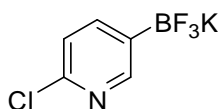
Saturated aqueous KHF_2 (1.69 g, 21.6 mmol), 6-methoxypyridin-3-ylboronic acid (1.0 g, 6.54 mmol) and methanol gave *potassium trifluoro(6-methoxypyridin-3-yl)borate* (1.25 g, 89 %) as a white solid; ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{CO}$): δ 3.79 (3H, s, OCH_3), 6.48 (1H, d, $^3J_{\text{HH}}$ 8.0, 5-*H*), 7.64 (1H, dd, $^3J_{\text{HH}}$ 8.0, $^4J_{\text{HH}}$ 1.5, 6-*H*), 8.16 (1H, s, 4-*H*); ^{13}C NMR (176 MHz; $(\text{CD}_3)_2\text{CO}$): δ 51.7, (OCH_3), 108.3 (5-*C*), 142.2 (4-*C*), 149.5 (2-*C*), 162.5 (6-*C*); ^{11}B NMR (225 MHz; $(\text{CD}_3)_2\text{CO}$): δ 3.15 (m); ^{19}F NMR (658 MHz, $(\text{CD}_3)_2\text{CO}$): δ -141.9 (m); m/z (ASAP $^+$) 157.1 ($[\text{M} - \text{KF}]^+$).

Potassium trifluoro(2-methoxypyridin-3-yl)borate (147)



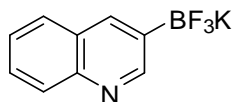
Saturated aqueous KHF_2 (1.69 g, 21.6 mmol) solution of 6-methoxypyridin-3-ylboronic acid (1.0 g, 6.54 mmol) and methanol gave *potassium trifluoro(2-methoxypyridin-3-yl)borate* (1.29 g, 92 %) as a white solid; ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{CO}$): δ 3.71 (3H, s, OCH_3), 6.59 (1H, dd, $^3J_{\text{HH}}$ 6.5, $^3J_{\text{HH}}$ 5.3, 5-*H*), 7.56–7.65 (1H, m, 6-*H*), 7.78 (1H, dd, $^3J_{\text{HH}}$ 4.9, $^3J_{\text{HH}}$ 2.1, 4-*H*); ^{13}C NMR (176 MHz; $(\text{CD}_3)_2\text{CO}$): 51.9 (OCH_3), 116.3 (5-*C*), 141.8 (4-*C*), 144.0 (6-*C*), 166.4 (2-*C*); ^{11}B NMR (225 MHz; $(\text{CD}_3)_2\text{CO}$): δ 3.11 (m); ^{19}F NMR (658 MHz, $(\text{CD}_3)_2\text{CO}$): δ -142.1 (m); m/z (ASAP $^+$) 185.1 ($[\text{M} - \text{KF}]^+$).

Potassium (6-chloropyridin-3-yl)trifluoroborate (149)



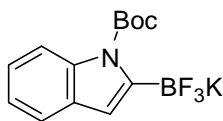
Saturated aqueous KHF_2 (1.64 g 21.0 mmol) solution of 6-chloropyridin-3-ylboronic acid (1.00 g, 6.35 mmol) and methanol gave *potassium (6-chloropyridin-3-yl)trifluoroborate* (1.22 g, 88 %) as white crystals; m.p. > 250 °C; ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{CO}$): δ 6.91 (1H, d, $^3J_{\text{HH}}$ 7.8, 5-*H*), 7.53 (1H, dd, $^3J_{\text{HH}}$ 7.7, $^4J_{\text{HH}}$ 1.5, 4-*H*), 8.15 (1H, s, 2-*H*); ^{13}C NMR (176 MHz; $(\text{CD}_3)_2\text{CO}$): δ 122.1 (5-*C*), 142.4 (4-*C*), 148.2 (2-*C*), 153.0 (6-*C*); ^{11}B NMR (225 MHz; $(\text{CD}_3)_2\text{CO}$): δ 2.94 (m); ^{19}F NMR (658 MHz, $(\text{CD}_3)_2\text{CO}$): δ -142.8 (m); m/z (ASAP $^+$) 161.1 ($[\text{M} - \text{KF}]^+$).

Potassium trifluoro(quinolin-3-yl)borate (151)



Saturated aqueous KHF_2 (1.49 g, 19.1 mmol), quinolin-3-ylboronic acid (1.00 g, 5.78 mmol) and methanol gave *potassium trifluoro(quinolin-3-yl)borate (X)* (1.21 g, 89 %) as white crystals; m.p. > 250 °C; ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{CO}$): δ 7.45 (1H, ddd, $^3J_{\text{HH}}$ 8.0, $^3J_{\text{HH}}$ 6.8, $^4J_{\text{HH}}$ 1.2, 6-*H*), 7.57 (1H, ddd, $^3J_{\text{HH}}$ 8.3, 6.8, $^4J_{\text{HH}}$ 1.4, 7-*H*), 7.81 (1H, d, $^3J_{\text{HH}}$ 8.1, 5-*H*), 7.94 (1H, d, $^3J_{\text{HH}}$ 8.4, 8-*H*), 9.01 (1H, s, 2-*H*); ^{13}C NMR (176 MHz; $(\text{CD}_3)_2\text{CO}$): δ ; 125.1 (4-*C*), 127.3 (Ar), 127.6 (Ar), 128.1 (Ar), 128.7 (Ar), 135.8 (2-*C*), 146.5 (4'-*C*), 155.1 (8'-*C*); ^{11}B NMR (225 MHz; $(\text{CD}_3)_2\text{CO}$): 3.26 (m); ^{19}F NMR (658 MHz, $(\text{CD}_3)_2\text{CO}$): δ -143.5 (m); m/z (ASAP $^+$) 177.0 ($[\text{M} - \text{KF}]^+$).

Potassium (1-(tert-butoxycarbonyl)-1H-indol-2-yl)trifluoroborate (153)



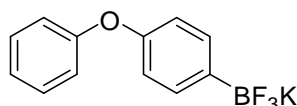
Saturated aqueous KHF_2 (0.987 g, 1.26 mmol), 1-(*tert*-butoxycarbonyl)-1H-indol-2-ylboronic acid (1.0 g, 3.83 mmol) and methanol gave *potassium (1-(tert-butoxycarbonyl)-1H-indol-2-yl)trifluoroborate* (1.09 g, 88 %) as white crystals; m.p. > 250 °C; ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{CO}$): δ 1.68 (9H, s, $\text{C}(\text{CH}_3)_3$), 6.63 (1H, s, 3-*H*), 7.00–7.13 (2H, m, 5-*H*, 6-*H*), 7.40 (1H, d, $^3J_{\text{HH}}$ 8.2, 4-*H*), 8.03 (1H, d, $^3J_{\text{HH}}$ 8.0, 7-*H*); ^{13}C NMR (176 MHz; $(\text{CD}_3)_2\text{CO}$) δ 27.8 ($\text{C}(\text{CH}_3)_3$), 82.3 ($\text{C}(\text{CH}_3)_3$), 113.1 (3-*C*), 115.1 (7-*C*), 119.7 (5-*C*), 121.6 (4-*C*), 122.1 (6-*C*), 131.8 (3'-*C*), 138.0 (7'-*C*), 151.8 (CO_2R); ^{11}B NMR (225 MHz; $(\text{CD}_3)_2\text{CO}$): 3.11 (m); ^{19}F NMR (658 MHz, $(\text{CD}_3)_2\text{CO}$): δ -139.8 (m); m/z (ASAP $^+$) 265.2 ($[\text{M} - \text{KF}]^+$).

7.3.2 Synthesis of Potassium Trifluoroborate Salts from Boronate Esters – General Procedure

A saturated aqueous solution of KHF_2 was added drop-wise to a concentrated solution of the boronate ester in methanol or acetone at room temperature and was left stirring for 30 min and a white precipitate formed. The solvents were evaporated to dryness to

give a white solid. The residue was re-dissolved in 50 % aq MeOH and all volatile materials were evaporated again. This process was repeated at least twice to give the desired trifluoroborate with no remaining boronate ester.⁶⁹ GC and NMR spectroscopy were used to check that the boronate ester had been converted fully

Potassium trifluoro(4-phenoxyphenyl)borate (102)

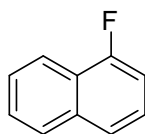


Saturated aqueous KHF_2 (0.870g, 11.1 mmol), 4-phenoxyphenyl boronic acid pinacol ester (1.00 g, 3.38 mmol) and methanol gave *potassium trifluoro(4-phenoxyphenyl)borate* (0.83 g, 89 %) as white crystals; m.p. > 200 °C; ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{CO}$) δ 6.78 (2H, d, $^2J_{\text{HH}}$ 7.7, 2-*H*), 6.91 (2H, dd, $^3J_{\text{HH}}$ 8.7, $^4J_{\text{HH}}$ 1.0, 2'-*H*), 7.00 (1H, tt, $^3J_{\text{HH}}$ 7.4, $^4J_{\text{HH}}$ 1.0, 4'-*H*), 7.29 (2H, dd, $^3J_{\text{HH}}$ 8.6, 7.4, 3'-*H*), 7.49 (2H, d, $^2J_{\text{HH}}$ 8.1, 3-*H*); ^{13}C NMR (176 MHz; $(\text{CD}_3)_2\text{CO}$) δ 117.5 (2-*C*), 121.9 (2'-*C*), 121.9 (3'-*C*), 133.0 (3-*C*), 154.4 (4'-*C*), 158.8 (1-*C*, 1'-*C*); ^{11}B NMR (225 MHz; $(\text{CD}_3)_2\text{CO}$): δ 3.10 (m); ^{19}F NMR (658 MHz, $(\text{CD}_3)_2\text{CO}$): δ -142.3 (m); m/z (ES^-) 237.1 ($[\text{M} - \text{K}]^+$).

7.3.3 Fluorination of Boronic acids/Trifluoroborates with Selectfluor™ – General Procedure

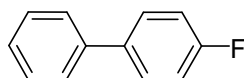
A solution of the boronic acid/ester/trifluoroborate (1 equiv.) and Selectfluor™ (1 equiv.) in acetonitrile (20 mL) was stirred at room temperature for 24 h. The reaction mixture was poured into water (30 mL) and extracted with DCM (3 x 30 mL). The combined organic layers were washed with saturated NaHCO_3 or NaCl (30 mL) and dried (MgSO_4) and the solvent removed by vacuum to give a crude product, which was analysed by ^{19}F NMR spectroscopy and GC-MS and purified by either column chromatography or recrystallisation. Where possible, the data was compared to the literature.

*1-Fluoronaphthalene (94)*¹¹⁹



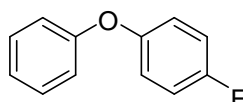
Potassium trifluoro(naphthalen-1-yl)borate (0.20 g, 0.855 mmol), Selectfluor™ (0.303 g, 0.855 mmol) and acetonitrile (20 mL) after purification by column chromatography with hexane and ethyl acetate (1:1) as the eluent gave *1-fluoronaphthalene* (0.087 g, 70 %) as a colourless oil; ¹H NMR (400 MHz, CDCl₃): δ 7.03–7.59 (4H, m, Ar-H), 7.76–8.06 (3H, m, Ar-H); ¹³C NMR (176 MHz, (CDCl₃): δ 109.6 (d, ²J_{CF} 19.8, 2-C), 120.7 (d, ³J_{CF} 5.1, Ar), 123.9 (d, ⁴J_{CF} 4.1, Ar), 125.8 (d, ³J_{CF} 8.3, Ar), 126.4 (d, ⁴J_{CF} 1.8, Ar), 127.0 (Ar), 127.7 (Ar), 128.1 (Ar), 135.1 (d, ³J_{CF} 4.8, Ar), 159.0 (d, ¹J_{CF} 251.5, 1-C); ¹⁹F NMR (188 MHz, CDCl₃): δ -123.9 (dd, ³J_{CF} 10.6, 5.4, ⁴J_{CF} 1.5); *m/z* (EI⁺) 145.8 ([M]⁺, 100 %), 125.0 (48), 120.0 (42), 73.0 (38).

*4-Fluorobiphenyl (100)*¹²⁰



Potassium biphenyl-4-yltrifluoroborate (0.50 g, 0.192 mmol), Selectfluor™ (0.681 g, 0.192 mmol) and acetonitrile (20 mL) after purification by column chromatography with hexane and ethyl acetate (9:1) as the eluent gave *4-fluorobiphenyl* (0.304 g, 92 %) as white crystals; m.p. 72–73 °C [lit. 73–74 °C]; ¹H NMR (700 MHz, CDCl₃): δ 7.15 (2H, m, 3-*H*), 7.34 – 7.66 (7H, m, Ar-H); ¹³C NMR (176 MHz, CDCl₃): δ 115.6 (d, ²J_{CF} 21.4, 2-C), 127.2 (Ar), 127.3 (Ar), 128.8 (Ar), 128.9 (Ar), 140.2 (Ar), 141.2 (Ar), 162.5 (d, ¹J_{CF} 246.3, 4-C); ¹⁹F NMR (658 MHz, CDCl₃): δ -115.8 (tt, ³J_{HF} 8.5, ⁴J_{HF} 5.3); *m/z* (EI⁺) 172.2 ([M]⁺, 100 %), 154.2 (92), 146.1 (24), 76.1 (48).

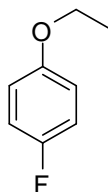
*1-Fluoro-4-phenoxybenzene (111)*¹²¹



Potassium trifluoro(4-phenoxyphenyl)borate (0.20 g, 0.724 mmol), Selectfluor™ (0.257 g, 0.724 mmol) and acetonitrile (20 mL) after purification by column chromatography with hexane and ethyl acetate (9:1) as the eluent gave *1-fluoro-4-phenoxybenzene*

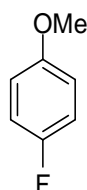
(0.103 g, 76 %) as a colourless oil; ^1H NMR (700 MHz, CDCl_3): δ 6.96–6.98 (5H, m, Ar-H), 7.30–7.40 (4H, m, Ar-H); ^{13}C NMR (176 MHz, CDCl_3): δ 116.3 (d, $^2J_{\text{CF}}$ 23.2, 2-C), 118.9 (2'-C), 120.5 (d, $^3J_{\text{CF}}$ 8.3, 3-C), 123.2 (4'-C), 129.7 (3'-C), 157.4 (4-C), 157.5 (1'-C), 158.8 (d, $^1J_{\text{CF}}$ 241.6, 1-C); ^{19}F NMR (658 MHz, CDCl_3): δ -120.5 (m); m/z (EI^+) 188.2 ($[\text{M}]^+$, 100 %), 159.1 (56), 77.1 (58).

1-Ethoxy-4-fluorobenzene (**112**)¹²²



Potassium trifluoro(4-ethoxyphenyl)borate (0.50 g, 2.19 mmol), SelectfluorTM (0.777 g, 2.19 mmol), 2,6-lutidine (0.235 g, 2.19 mmol) and acetonitrile (20 mL) after purification by column chromatography with hexane and ethyl acetate (1:1) as the eluent gave *1-ethoxy-4-fluorobenzene* (0.219 g, 71 %) as a colourless oil; ^1H NMR (700 MHz, CDCl_3): δ 1.26 (3H, t, $^3J_{\text{HH}}$ 7.0, CH_2CH_3), 3.86 (2H, q, $^3J_{\text{HH}}$ 7.0, CH_2CH_3), 6.68–6.84 (4H, m, Ar-H); ^{13}C NMR (176 MHz, CDCl_3): δ 14.8 (CH_2CH_3), 63.9 (CH_2CH_3), 115.3 (d, $^3J_{\text{CF}}$ 8.0, 3-C), 115.7 (d, $^2J_{\text{CF}}$ 23.0, 2-C), 155.0 (1-C), 157.1 (d, $^1J_{\text{CF}}$ 237.8, 4-C); ^{19}F NMR (658 MHz, CDCl_3): δ -124.8 (tt, $^3J_{\text{HF}}$ 2.3, $^4J_{\text{HF}}$ 4.3); m/z (EI^+) 140.0 ($[\text{M}]^+$, 100 %), 112.1 (90), 83.4 (91), 57.1 (34).

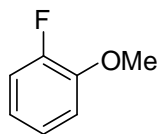
1-Fluoro-4-methoxybenzene (**115**)¹²³



Potassium trifluoro(4-methoxyphenyl)borate (0.30 g, 1.40 mmol), SelectfluorTM (0.50 g, 1.40 mmol) and acetonitrile (20 mL) after purification by column chromatography with hexane/ethyl acetate (9:1) as the eluent gave *1-fluoro-4-methoxybenzene* (0.177 g, 71 %) as a colourless oil; ^1H NMR (700 MHz, CDCl_3): δ 3.77 (3H, s, OCH_3), 6.82–6.84 (2H, m, 3-H), 6.95–6.99 (2H, m, 2-H); ^{13}C NMR (176 MHz, CDCl_3): δ 55.7 (OCH_3), 114.7 (d, $^3J_{\text{CF}}$ 7.9, 3-C), 115.7 (d, $^2J_{\text{CF}}$ 23.1, 2-C), 155.7 (4-C), 156.5 (d, $^1J_{\text{CF}}$ 237.8, 1-

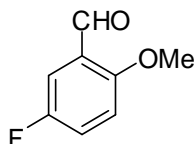
C); ^{19}F NMR (658 MHz, CDCl_3): δ -125.2 (tt, $^3J_{\text{CF}}$ 8.3, $^4J_{\text{CF}}$ 4.3); m/z (EI^+) 126.1 ($[\text{M}]^+$, 100 %), 111.1 (88), 83.0 (94), 57.1 (44).

*1-Fluoro-2-methoxybenzene (117)*³⁴



Potassium trifluoro(2-methoxyphenyl)borate (0.30 g, 1.40 mmol), SelectfluorTM (0.50 g, 1.40 mmol) and acetonitrile (20 mL) after purification by column chromatography with hexane and ethyl acetate (7:3) as the eluent gave *1-fluoro-2-methoxybenzene (X)* (0.99 g, 56 %) as a colourless oil; (Found $[\text{MH}]^+$ 127.0548 $\text{C}_7\text{H}_7\text{FO}$ requires: $[\text{MH}]^+$ 127.0559); ^1H NMR (600 MHz, CDCl_3): δ 3.91 (3H, s, OCH_3) 6.62–6.66 (1H, m, 3-*H*), 6.71 (1H, td, $^3J_{\text{HH}}$ 8.6, $^4J_{\text{HF}}$ 1.4, 5-*H*), 6.79–6.86 (2H, m, 4-*H*, 6-*H*); ^{13}C NMR (151 MHz, CDCl_3): δ 56.1 (OCH_3), 113.5 (4-*C*), 115.9 (d, $^2J_{\text{CF}}$ 18.1, 6-*C*), 120.9 (d, $^3J_{\text{CF}}$ 6.8, 3-*C*), 124.3 (d, $^3J_{\text{CF}}$ 3.9, 5-*C*), 147.7 (d, $^2J_{\text{CF}}$ 10.5, 2-*C*), 152.5 (d, $^1J_{\text{CF}}$ 245.1, 1-*C*); ^{19}F NMR (564 MHz, CDCl_3): δ -135.7 (m); m/z (EI^+) 126.0 ($[\text{M}]^+$, 100 %), 111.0 (80), 83.0 (94), 57.1 (58).

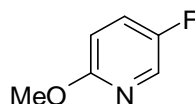
*5-Fluoro-2-methoxybenzaldehyde (138)*¹²⁴



Potassium trifluoro(3-formyl-4-methoxyphenyl)borate (0.50 g, 2.07 mmol), SelectfluorTM (0.732 g, 2.07 mmol) and acetonitrile (20 mL) after purification by column chromatography with hexane and ethyl acetate (9:1) as the eluent gave *5-fluoro-2-methoxybenzaldehyde* (0.198 g, 62 %) as a colourless oil; m.p. 48–49 °C [lit. 47–48 °C]; (Found $[\text{MH}]^+$ 155.0500 $\text{C}_8\text{H}_7\text{FO}_2$ requires: $[\text{MH}]^+$ 155.0430); ^1H NMR (600 MHz, CDCl_3): δ 3.90 (3H, s, OCH_3), 6.94 (1H, dd, $^3J_{\text{HH}}$ 9.1, $^4J_{\text{HF}}$ 3.8, 3-*H*), 7.23 (1H, td, $^3J_{\text{HH}}$ 9.1, $^3J_{\text{HF}}$ 7.5, $^4J_{\text{HH}}$ 3.2, 4-*H*), 7.48 (1H, dd, $^3J_{\text{HF}}$ 8.2, $^4J_{\text{HH}}$ 3.3, 6-*H*), 10.4 (1H, d, $^5J_{\text{HF}}$ 3.2, CHO); ^{13}C NMR (151 MHz, CDCl_3): δ 56.2 (OCH_3), 113.1 (d, $^3J_{\text{CF}}$ 7.2, 3-*C*), 114.0 (d, $^2J_{\text{CF}}$ 23.5, 4-*C*), 122.4 (d, $^2J_{\text{CF}}$ 23.9, 6-*C*), 125.5 (d, $^3J_{\text{CF}}$ 5.9, 1-*C*), 156.9 (d, $^1J_{\text{CF}}$ 241.2, 5-*C*), 158.1 (d, $^4J_{\text{CF}}$ 1.8, 2-*C*), 188.7 (d, $^4J_{\text{CF}}$ 1.7, CHO); ^{19}F NMR (564 MHz, CDCl_3): δ

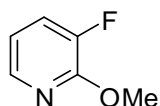
-122.8 (ddd, $^3J_{\text{HF}}$ 11.4, $^3J_{\text{HF}}$ 7.6, $^4J_{\text{HF}}$ 3.5); m/z (EI^+) 154.0 ($[\text{M}]^+$, 100 %), 136.0 (73), 110.0 (56), 83.0 (86), 57.7 (57).

5-Fluoro-2-methoxypyridine (146)



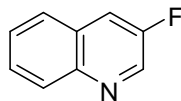
Potassium trifluoro(6-methoxypyridin-3-yl)borate (0.50 g, 2.33 mmol), Selectfluor™ (0.824 g, 2.33 mmol) and acetonitrile (20 mL) after purification by column chromatography with hexane and ethyl acetate (7:3) as the eluent gave *1-fluoro-3-methoxybenzene* (0.10 g, 34 %) as a pale yellow oil; (Found $[\text{MH}]^+$ 128.0517 $\text{C}_6\text{H}_6\text{FNO}$ requires: $[\text{MH}]^+$ 128.0512); ^1H NMR (700 MHz, CDCl_3): δ 3.87 (3H, s, OCH_3) 6.46 (1H, dd, $^3J_{\text{HH}}$ 8.6, $^4J_{\text{HH}}$ 3.6, 6-*H*), 7.11 (1H, ddd, $^3J_{\text{HH}}$ 9.0, $^3J_{\text{HH}}$ 7.6, $^4J_{\text{HH}}$ 3.1, 4-*H*), 7.71 (1H, d, $^3J_{\text{HH}}$ 3.1, 2-*H*); ^{13}C NMR (176 MHz, (CDCl_3): δ 60.7 (OCH_3), 111.6 (3-*C*), 126.7 (d, $^2J_{\text{CF}}$ 21.4, 4-*C*), 133.2 (d, $^2J_{\text{CF}}$ 26.0, 6-*C*), 155.6 (d, $^1J_{\text{CF}}$ 245.1, 5-*C*), 160.5 (2-*C*); ^{19}F NMR (658 MHz, CDCl_3): δ -139.8 (m); m/z (EI^+) 126.0 ($[\text{M}]^+$, 100 %), 97.1 (80), 70.1 (71), 57.1 (58).

3-Fluoro-2-methoxypyridine (148)



Potassium trifluoro(2-methoxypyridin-3-yl)borate (0.50 g, 2.33 mmol), Selectfluor™ (0.824 g, 2.33 mmol) and acetonitrile (20 mL) after purification by column chromatography with hexane and ethyl acetate (7:3) as the eluent gave *3-fluoro-2-methoxypyridine* (0.107 g, 36 %) as a colourless oil; (Found $[\text{MH}]^+$ 128.0514 $\text{C}_6\text{H}_6\text{FNO}$ requires: $[\text{MH}]^+$ 128.0512); ^1H NMR (700 MHz, CDCl_3): δ 3.90 (3H, s, OCH_3) 6.79–6.88 (1H, ddd, $^3J_{\text{HH}}$ 8.0, $^4J_{\text{HH}}$ 5.0, $^4J_{\text{HF}}$ 3.2, 5-*H*), 7.15–7.28 (1H, ddd, $^3J_{\text{HH}}$ 10.4, $^3J_{\text{HH}}$ 7.8, $^4J_{\text{HH}}$ 1.6, 6-*H*), 7.77–7.83 (1H, dd, $^3J_{\text{HH}}$ 5.0, $^3J_{\text{HF}}$ 1.5, 4-*H*); ^{13}C NMR (176 MHz, (CDCl_3): δ 53.4 (OCH_3), 116.5 (d, $^3J_{\text{CF}}$ 2.0, 5-*C*), 122.5 (d, $^2J_{\text{CF}}$ 15.4, 4-*C*), 114.1 (6-*C*), 148.6 (d, $^1J_{\text{CF}}$ 258.4, 3-*C*), 153.1 (d, $^2J_{\text{CF}}$ 10.9, 2-*C*); ^{19}F NMR (658 MHz, CDCl_3): δ -139.9 (m); m/z (EI^+) 126.0 ($[\text{M}]^+$, 100 %), 97.1 (80), 70.1 (71), 57.1 (58).

3-Fluoroquinoline (**152**)



Potassium trifluoro(quinolin-3-yl)borate (0.30 g, 1.28 mmol), Selectfluor™ (0.45 g, 1.28 mmol) and acetonitrile (20 mL) after purification by column chromatography with hexane and ethyl acetate (1:1) as the eluent to give 3-fluoroquinoline (0.087 g, 46 %) as a colourless oil; (Found $[M]^+$, 148.0540. C_9H_6FN requires: $[M]^+$, 148.0563); 1H NMR (500 MHz, $CDCl_3$): δ 7.57 (1H, m, 4-*H*), 7.68 (1H, m, Ar), 7.74–7.81 (2H, m, Ar), 8.12 (1H, m, Ar), 8.82 (1H, d, $^3J_{HF}$ 8.5, 2-*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 118.6 (d, $^2J_{CF}$ 16.4, 4-*C*), 127.5 (d, $^3J_{CF}$ 5.1, 5-*C*), 127.9 (Ar), 128.7 (d, $^4J_{CF}$ 5.4, 8-*C*), 128.8 (Ar), 129.6 (Ar), 141.7 (d, $^2J_{CF}$ 27.3, 2-*C*), 146 (Ar), 156.5 (d, $^1J_{CF}$ 256.2, 3-*C*); ^{19}F NMR (376 MHz, $CDCl_3$): δ -128.7 (m); m/z (EI^+) 147.1 ($[M]^+$, 100 %), 127.1 (48), 99.1 (50), 74.0 (79), 50.1 (94).

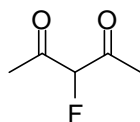
7.4 Experimental to Chapter 4

7.4.1 Direct Fluorination of 1,3-Diketones Using Flow Reactor - General Procedure

After purging the continuous flow apparatus with nitrogen, fluorine, as a 10 % mixture in nitrogen (v:v), was passed through the microreactor via an inlet port at a prescribed flow-rate (15 mL/ min) that was controlled by a Brooks Instruments™ mass flow controller. The microreactor was cooled by an external cryostat to 5–10 °C. The substrate solution (1 mL/ h) in formic acid or MeCN (4 mL) was injected by a mechanised syringe pump into the microreactor channel at a prescribed flow rate through the substrate inlet port. After passing through the microreactor and outlet port, excess fluorine gas and volatile waste products were passed through a scrubber filled with soda lime. Products were collected in a PTFE collection. ^{19}F NMR spectroscopic analysis of the reaction mixture determined if any fluorination had occurred. The product was then washed by water (30 mL) and extracted by DCM (3 x 30 mL). The organic extracts were then washed with saturated $NaHCO_3$ (50 mL) and dried over $MgSO_4$ and the solvent removed by vacuum to give a crude product, which was

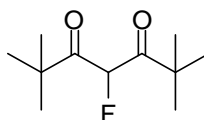
analysed by ^{19}F NMR spectroscopy and GC-MS and purified by either column chromatography, distillation or recrystallisation, if required.

*3-Fluoropentane-2,4-dione (180)*¹⁰¹



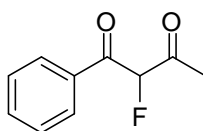
Pentane-2,4-dione (0.40 g, 4.0 mmol), formic acid (4 mL) and F_2 (16 mmol) after purification by distillation gave *3-fluoropentane-2,4-dione* as a colourless oil (0.389 g, 82 %); b.p. 136–140 °C [lit.⁹⁴ 50 °C/10 Torr]; ^1H NMR (700 MHz, CDCl_3): δ 2.25 (6H, s, CH_3), 5.23 (1H, d, $^2J_{\text{HF}}$ 50.2, 3-*H*); ^{13}C NMR (176 MHz, (CDCl_3)): δ 25.6 (1-*C*), 124.5 (3-*C*), 217.5 (2-*C*, 4-*C*); ^{19}F NMR (658 MHz, CDCl_3) δ -191.6 (d, $^2J_{\text{HF}}$ 51.0); m/z (EI^+) 117.9 ($[\text{M}^+]$, 100 %), 84.9 (36), 42.7 (100); as compared to the literature.

*4-Fluoro-2,2,6,6-tetramethylheptane-3,5-dione (188)*¹²⁵



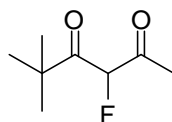
2,2,6,6-Tetramethylheptane-3,5-dione (0.184 g, 1.0 mmol), acetonitrile (4 mL) and F_2 (16 mmol) gave *4-fluoro-2,2,6,6-tetramethylheptane-3,5-dione* (0.172 g, 85 %) as a colourless oil; (Found $[\text{MH}]^+$, 202.1282. $\text{C}_{11}\text{H}_{19}\text{FO}_2$ requires: $[\text{MH}]^+$, 202.1389); ^1H NMR (700 MHz, CDCl_3): δ 1.19 (18H, s, $\text{C}(\text{CH}_3)_3$), 5.69 (1H, d, $^2J_{\text{HF}}$ 48.8, 4-*H*); ^{13}C NMR (176 MHz, (CDCl_3)) δ 25.8 (d, $\text{C}(\underline{\text{CH}_3})_3$), 44.7 ($\underline{\text{C}}(\text{CH}_3)_3$), 92.8 (d, $^1J_{\text{CF}}$ 189.9, 4-*C*), 207.6 (d, $^2J_{\text{CF}}$ 17.8, 2-*C*, 6-*C*); ^{19}F NMR (658 MHz, CDCl_3) δ -186.6 (d, $^2J_{\text{HF}}$ 48.8); m/z (ES^+) 225.0 $[\text{M} + \text{Na}]^+$; as compared to the literature. This was used without further purification in subsequent reactions.

*2-Fluoro-1-phenylbutane-1,3-dione (189)*¹²⁶



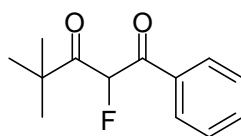
1-Phenylbutane-1,3-dione (0.162 g, 1.00 mmol), formic acid (4 mL) and F₂ (16 mmol) after recrystallisation from ethanol gave *2-fluoro-1-phenylbutane-1,3-dione* (0.121 g, 87 %) as colourless crystals; m.p. 55–57 °C [lit. 58–59 °C]; ¹H NMR (700 MHz, CDCl₃): δ 2.31 (3H, d, ³J_{HF} 4.5, CH₃), 5.82 (1H, d, ¹J_{HF} 50.1, 2-*H*), 7.45–7.54 (2H, m, Ar-*H*), 7.58–7.68 (1H, m, Ar-*H*), 7.97–8.06 (2H, m, Ar-*H*); ¹³C NMR (176 MHz, (CDCl₃)): δ 25.9 (CH₃), 96.5 (d, ¹J_{CF} 198.2, 2-*C*), 128.7 (Ar), 128.9 (Ar), 134.6 (Ar), 129.6 (d, ³J_{CF} 3.1, Ar), 195.9 (d, ²J_{CF} 27.7, 3-*C*), 200.5 (d, ²J_{CF} 23.8, 1-*C*); ¹⁹F NMR (658 MHz, CDCl₃): δ -194.1 (d, ²J_{HF} 51.1); *m/z* (EI⁺) 180.1 ([M]⁺, 100 %), 138.0 (44), 105.0 (100), 76.9 (98), 43.0 (64); as compared to the literature.

3-Fluoro-5,5-dimethylhexane-2,4-dione (**190**)



5,5-Dimethylhexane-2,4-dione (0.160 g, 1.0 mmol), acetonitrile (4 mL) and F₂ (16 mmol) gave *3-fluoro-5,5-dimethylhexane-2,4-dione* (0.143 g, 89 %) as a colourless oil; (Found [MH]⁺, 161.0970. C₈H₁₃FO₂ requires: [MH]⁺, 161.0978); ¹H NMR (400 MHz, CDCl₃): δ 1.12 (9H, d, ⁵J_{HF} 1.0, C(CH₃)₃), 2.20 (3H, d, ⁴J_{HF} 4.1, CH₃), 5.41 (1H, d, ²J_{HF} 49.1, 3-*H*); ¹³C NMR (176 MHz, (CDCl₃)): δ 25.6 (d, ⁴J_{CF} 2.5, C(CH₃)₃), 26.0 (d, ³J_{CF} 4.2, CH₃), 44.8 (d, ³J_{CF} 2.2, C(CH₃)₃), 95.7 (d, ¹J_{CF} 198.9, 3-*C*), 200.7 (d, ²J_{CF} 23.3, 4-*C*), 206.0 (d, ²J_{CF} 17.4, 2-*C*); ¹⁹F NMR (658 MHz, CDCl₃): δ -188.4 (d, ²J_{HF} 50.2); *m/z* (EI⁺) 160.1 ([M]⁺, 100 %), 103.0 (49), 85.1 (45), 57.0 (100); *3,3-difluoro-5,5-dimethylhexane-2,4-dione*: ¹H NMR (400 MHz, CDCl₃): δ 1.15 (9H, m, C(CH₃)₃), 2.28 (3H, s, CH₃); ¹⁹F NMR (658 MHz, CDCl₃): δ -109.5 (s).

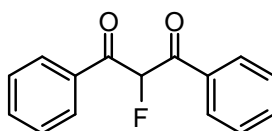
2-Fluoro-4,4-dimethyl-1-phenylpentane-1,3-dione (**191**)



4,4-Dimethyl-1-phenylpentane-1,3-dione (0.204 g, 1.0 mmol), acetonitrile (4 mL) and F₂ (16 mmol) gave *2-fluoro-4,4-dimethyl-1-phenylpentane-1,3-dione* (0.187 g, 84 %) as

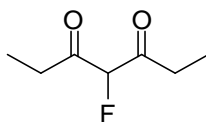
a colourless oil; (Found $[\text{MH}]^+$, 223.1137. $\text{C}_{13}\text{H}_{15}\text{FO}_2$ requires: $[\text{MH}]^+$, 223.1134); ^1H NMR (400 MHz, CDCl_3): δ 1.18 (9H, d, $^5J_{\text{HF}}$ 1.0, $\text{C}(\text{CH}_3)_3$), 6.09 (1H, d, $^2J_{\text{HF}}$ 49.2, 2-*H*), 7.40 (3H, m, Ar-H), 7.53 (1H, tt, $^3J_{\text{HF}}$ 7.4, $^5J_{\text{HF}}$ 1.3, Ar-H), 7.93 (2H, dm, $^3J_{\text{HF}}$ 8.4, Ar-H); ^{13}C NMR (176 MHz, CDCl_3): δ 26.0 (d, $^4J_{\text{CF}}$ 2.6, $\text{C}(\text{CH}_3)_3$), 44.9 (d, $^3J_{\text{CF}}$ 2.4, $\text{C}(\text{CH}_3)_3$), 94.9 (d, $^1J_{\text{CF}}$ 199.0, 2-C), 128.7 (Ar), 129.7 (d, $^3J_{\text{CF}}$ 3.5, Ar), 134.2 (Ar), 191.5 (d, $^2J_{\text{CF}}$ 20.1, 1-C), 206.8 (d, $^2J_{\text{CF}}$ 18.3, 3-C); ^{19}F NMR (658 MHz, CDCl_3): δ -187.2 (d, $^2J_{\text{HF}}$ 49.2); m/z (EI^+) 222.1 ($[\text{M}]^+$, 100 %), 165.1 (49), 138.1 (66), 105.1 (74), 57.1 (100); This was used without further purification in subsequent reactions.

2-Fluoro-1,3-diphenylpropane-1,3-dione (**192**)¹²⁷



1,3-Diphenylpropane-1,3-dione (0.224 g, 1.0 mmol), formic acid (20 mL) and F_2 (16 mmol) after purification by recrystallisation from hexane gave *2-fluoro-1,3-diphenylpropane-1,3-dione* (0.133 g, 55 %) as yellow crystals; m.p. 68–69 °C [lit. 67–68 °C]; ^1H NMR (700 MHz, CDCl_3): δ 6.41 (1H, d, $^2J_{\text{HF}}$ 49.1, 2-*H*), 7.44–7.58 (4H, m, Ar-H), 8.06–8.12 (6H, m, Ar-H); ^{13}C NMR (176 MHz, CDCl_3): δ 116.6 (d, $^1J_{\text{CF}}$ 196.1, 2-C), 124.5 (Ar), 136.1 (Ar), 138.2 (Ar), 201.5 (1-C/3-C); ^{19}F NMR (658 MHz, CDCl_3): δ -187.1 (d, $^2J_{\text{HF}}$ 50.4); m/z (EI^+); 242.1 ($[\text{M}]^+$, 100 %), 224.1 (62), 148.3 (47), 106.7 (100); as compared to the literature.

4-Fluoroheptane-3,5-dione (**193**)¹²⁸



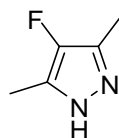
Heptane-3,5-dione (0.128 g, 1.0 mmol), acetonitrile (4 mL) and F_2 (16 mmol) gave *4-fluoroheptane-3,5-dione* (0.121 g, 83 %) as a colourless oil; (Found $[\text{MH}]^+$, 147.0816. $\text{C}_7\text{H}_{11}\text{FO}_2$ requires: $[\text{MH}]^+$, 147.0821); ^1H NMR (400 MHz, CDCl_3): δ 1.00 (6H, dt, $^3J_{\text{HH}}$ 7.2, $^5J_{\text{HF}}$ 1.2, CH_2CH_3), 2.36–2.77 (4H, m, CH_2CH_3), 5.21 (1H, d, $^2J_{\text{HF}}$ 50.3, 4-*H*); ^{13}C NMR (176 MHz, CDCl_3): δ 6.62 (d, $^4J_{\text{CF}}$ 2.1, CH_2CH_3), 32.1 (CH_2CH_3), 97.9 (d,

$^1J_{\text{CF}}$ 199.5, 4-*C*), 202.1 (d, $^2J_{\text{CF}}$ 21.5, 3-*C*/5-*C*); ^{19}F NMR (658 MHz, CDCl_3): δ -195.6 (d, $^2J_{\text{HF}}$ 50.1); m/z (EI^+) 146.1 ($[\text{M}^+]$, 100 %), 117.1 (55), 57.1 (100), 29.2 (38); as compared to the literature. This was used without further purification in subsequent reactions.

7.4.2 Step-wise Synthesis of 4-Fluoropyrazoles - General Procedure

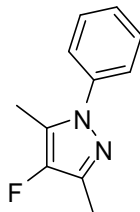
Hydrazine monohydrate or phenyl hydrazine (1.0 equiv.) was added slowly to a mixture of the 2-fluoro-1,3-diketone (1.0 equiv.), ethanol (30 mL) and conc. H_2SO_4 (~0.5 mL). The reaction was heated to reflux for 6–24 h. On cooling, the solvent was evaporated and water added (50 mL). The organic products were extracted with DCM (3 x 30 mL) and washed with water (30 mL) and NaCl solution (30 mL). The combined extracts were dried (MgSO_4), filtered and the solvent removed by vacuum to give a crude product, which was analysed by ^{19}F NMR spectroscopy and GC-MS and purified by either column chromatography or recrystallisation.

4-Fluoro-3,5-dimethyl-1H-pyrazole (194)



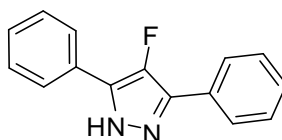
3-Fluoropentane-2,4-dione (0.30 g, 2.54 mmol), hydrazine monohydrate (0.140 g, 2.79 mmol) and ethanol (30 mL) after purification by column chromatography over silica gel with hexane and ethyl acetate (1:1) as the eluent gave *4-fluoro-3,5-dimethyl-1H-pyrazole* (0.221 g, 76 %) as pale yellow crystals; m.p. 107–109 °C [lit.¹²⁹ 108–110 °C]; (Found $[\text{MH}]^+$, 115.0667. $\text{C}_5\text{H}_7\text{FN}_2$ requires: $[\text{MH}]^+$, 115.0672); ^1H NMR (400 MHz; CDCl_3): δ 2.26 (6H, s, CH_3), 8.61 (1H, bs, NH); ^{13}C NMR (126 MHz; CDCl_3): δ 9.1 (d, $^2J_{\text{CF}}$ 2.9, CH_3), 129.6 (3-*C*/5-*C*), 143.5 (1F, d, $^1J_{\text{CF}}$ 239.8, 4-*C*); ^{19}F NMR (376 MHz; CDCl_3): δ -183.4 (s); m/z (EI^+) 114.1 ($[\text{M}]^+$, 100 %), 113.0 (82), 41.9 (79).

4-Fluoro-3,5-dimethyl-1-phenyl-1H-pyrazole (195)



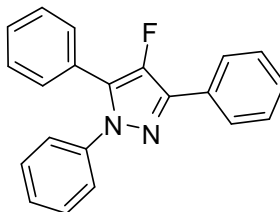
3-Fluoropentane-2,4-dione (0.30 g, 2.54 mmol), phenyl hydrazine (0.302 g, 2.79 mmol) and ethanol (30 mL) after purification by column chromatography over silica gel with hexane and ethyl acetate (7:3) as the eluent gave *4-fluoro-3,5-dimethyl-1-phenyl-1H-pyrazole* (0.351 g, 73 %) as a yellow oil; (Found: $[M]^+$, 190.0906. $C_{15}H_{11}FN_2$ requires: $[M]^+$, 190.0906); 1H NMR (400 MHz; $CDCl_3$): δ 2.35 (3H, s, CH_3), 2.37 (3H, s, CH_3), 7.20–7.50 (5H, m, Ar-H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 9.7 (d, $^3J_{CF}$ 3.1, CH_3), 10.3 (d, $^3J_{CF}$ 3.0, CH_3), 124.4 (3'-C), 127.6 (4'-C), 129.4 (2'-C), 135.9 (d, $^2J_{CF}$ 11.2, 3-C, 5-C), 140.1 (1'-C), 146.8 (d, $^1J_{CF}$ 243.4, 4-C); ^{19}F NMR (376 MHz; $CDCl_3$): δ -179.9 (s); m/z (EI^+) 190.2 ($[M]^+$, 100 %), 148.0 (24), 118.1 (32), 77.0 (50).

4-Fluoro-3,5-diphenyl-1H-pyrazole (196)



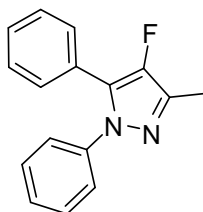
2-Fluoro-1,3-diphenylpropane-1,3-dione (0.30 g, 1.24 mmol), hydrazine monohydrate (0.068 g, 1.36 mmol) and ethanol (30 mL) after purification by column chromatography with DCM as to eluent gave *4-fluoro-3,5-diphenyl-1H-pyrazole* (0.234 g, 79 %) as pale yellow crystals; m.p. 185–188 °C; (Found $[MH]^+$, 239.0972. $C_{15}H_{11}FN_2$ requires: $[MH]^+$, 239.0983); 1H NMR (400 MHz; $CDCl_3$): δ 7.41–7.47 (2H, m, 4'-H), 7.48–7.51 (4H, m, 3'-H), 7.77–7.80 (4H, m, 2'-H), 10.3 (1H, bs, NH), ^{13}C NMR (126 MHz; $CDCl_3$): δ 128.2 (2'-C), 129.0 (4'-C), 129.3 (3-C), 131.1 (d, $^2J_{CF}$ 15.0, 1-C, 3-C), 140.0 (d, $^1J_{CF}$ 226.6, 4-C), 148.7 (1'-C), ^{19}F NMR (376 MHz; $CDCl_3$): δ -174.3 (s); m/z (EI^+) 237.9 ($[M]^+$, 100 %), 107.8 (43), 76.9 (40).

4-Fluoro-1,3,5-triphenyl-1H-pyrazole (197)



2-Fluoro-1,3-diphenylpropane-1,3-dione (0.30 g, 1.24 mmol), phenyl hydrazine (0.147 g, 1.36 mmol) and ethanol (30 mL) after purification by column chromatography with DCM as the eluent gave *4-fluoro-1,3,5-triphenyl-1H-pyrazole* (0.314 g, 81 %) as orange crystals; m.p. 141–143 °C [lit.⁹⁴ 141–142 °C]; (Found $[MH]^+$, 315.1293. $C_{10}H_9FN_2$ requires: $[MH]^+$, 315.1296); 1H NMR (400 MHz; $CDCl_3$): δ 7.34–7.28 (3H, m, Ar-H), 7.34–7.38 (6H, m, Ar-H), 7.43–7.48 (2H, m, Ar-H), 8.00 (4H, Ar-H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 128.6 (Ar), 128.7 (Ar), 128.8 (Ar), 129.0 (Ar), 129.1 (Ar), 129.2 (Ar), 129.4 (Ar), 130.7 (Ar), 130.8 (Ar), 138.3 (Ar), 138.4 (3-C), 140.0 (5-C), 145.7 (d, $^1J_{CF}$ 253.9, 4-C); ^{19}F NMR (376 MHz; $CDCl_3$): δ -172.5 (s); m/z (EI^+) 314.2 ($[M]^+$, 100 %), 293.1 (70), 190.1 (25), 133.7 (16), 77.0 (66), 51.1 (20).

4-Fluoro-5-methyl-1,3-diphenyl-1H-pyrazole (198)



2-Fluoro-1-phenylbutane-1,3-dione (0.40 g, 2.22 mmol), phenyl hydrazine (0.24 g, 2.22 mmol) and ethanol (20 mL) after purification by column chromatography with DCM as the eluent gave *4-fluoro-5-methyl-1,3-diphenyl-1H-pyrazole* (0.47 g, 84 %) as a yellow oil; (Found $[M]^+$, 252.1063. $C_{16}H_{13}FN_2$ requires: $[M]^+$, 252.1070); 1H NMR (400 MHz; $CDCl_3$): δ 2.37 (3H, s, CH_3), 7.23–7.27 (10H, m, Ar-H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 10.3 (d, $^3J_{CF}$ 3, CH_3), 125.0 (Ar), 127.5 (Ar), 127.8 (d, $^2J_{CF}$ 4.0, 5-C), 128.8 (Ar), 129.0 (Ar), 129.1 (Ar), 129.2 (Ar), 136.7 (d, $^2J_{CF}$ 11.5, 3-C), 140.3 (Ar), 146.7 (d, $^1J_{CF}$ 249.3, 4-C), 155.9 (Ar); ^{19}F NMR (376 MHz; $CDCl_3$): δ -177.3 (s); m/z (EI^+) 252.2 ($[M]^+$, 100 %), 231.1 (32), 180.1 (18), 108.1 (14), 77.0 (48).

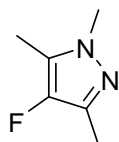
7.4.3 Two-Step Continuous Flow Fluoropyrazole Process - General Procedure

After purging the continuous flow reactor apparatus with nitrogen, fluorine, as a 10 % mixture in nitrogen (v:v), was passed through the flow reactor via an Input A at a prescribed flow-rate (18 mL/ min) which was controlled by a Brooks Instruments™ gas mass flow controller. The flow reactor was cooled by an external cryostat to 5–10 °C. The diketone solution was injected by a mechanised syringe pump into the flow reactor channel at a prescribed flow-rate (2 mL/ h) through the substrate Input B. At the same time, the hydrazine mixture was injected via Input C by a mechanised syringe pump into the flow reactor via a T-piece at a prescribed flow-rate (2 mL/ h). All flow streams were passed through the reactor and the product mixture was collected in a vessel containing water. The collected mixture was then extracted from DCM (3 x 30 mL) and washed with sodium bicarbonate (30 mL) and water (30 mL). The combined extracts were dried over MgSO₄ and the solvent removed by vacuum to give a crude product, which was analysed by ¹⁹F NMR spectroscopy and GC-MS and purified by either column chromatography or recrystallisation.

4-Fluoro-3,5-dimethyl-1H-pyrazole (194)

Pentane-2,4-dione (0.10 g, 1.0 mmol) in MeCN (4 mL, 2 mL/ h), fluorine (18 mL/ min), and methyl hydrazine (0.07 g, 1.5 mmol) in ethanol (4 mL, 2 mL/h) after purification by column chromatography on silica gel with 1:1 hexane and ethyl acetate as the eluent, gave *4-fluoro-3,5-dimethyl-1H-pyrazole* (0.075 g, 66 %) as pale yellow crystals; spectral and physical data as above.

4-Fluoro-1,3,5-trimethyl-1H-pyrazole (199)



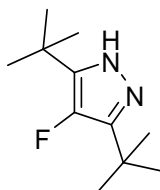
Pentane-2,4-dione (0.10 g, 1.0 mmol), MeCN (4 mL) and F₂ (9.6 mmol) with methyl hydrazine (0.0691 g, 1.5 mmol), ethanol (4 mL) after recrystallisation from hexane gave *4-fluoro-1,3,5-trimethyl-1H-pyrazole* (0.094 g, 73 %) as yellow crystals; m.p. 83–85

°C; (Found: $[M - H]^+$, 127.0866. $C_6H_9FN_2$ requires: $[M - H]^+$, 127.0871); 1H NMR (700 MHz, $CDCl_3$): δ 1.53 (3H, s, CH_3), 1.78 (3H, s, CH_3), 3.26 (3H, s, NCH_3); ^{13}C NMR (176 MHz, $CDCl_3$): δ 7.94 (d, $^3J_{CF}$ 3.1, CH_3), 9.77 (d, $^3J_{CF}$ 3.0, CH_3), 36.4 (NCH_3), 123.7 (d, $^2J_{CF}$ 25.8, 3-C), 133.0 (d, $^2J_{CF}$ 10.9, 5-C), 145.4 (d, $^1J_{CF}$ 241.1, 4-C); ^{19}F NMR (658 MHz, $CDCl_3$): δ -181.4 (s); m/z (ES^+) 128.8.

4-Fluoro-3,5-dimethyl-1-phenyl-1H-pyrazole (195)

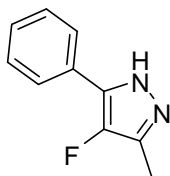
Pentane-2,4-dione (0.10 g, 1.0 mmol) in MeCN (4 mL, 2 mL/ h), fluorine (18 mL/ min) and phenyl hydrazine (0.162 g, 1.5 mmol) in ethanol (4 mL, 2 mL/ h) after purification by column chromatography on silica gel with 1:1 hexane and ethyl acetate as the eluent, gave *4-fluoro-3,5-dimethyl-1-phenyl-1H-pyrazole* (0.137 g, 72 %) as a yellow oil; spectral and physical data as above.

3,5-Di-tert-butyl-4-fluoro-1H-pyrazole (200)



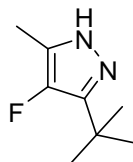
2,2,6,6-Tetramethylheptane-3,5-dione (0.184 g, 1.0 mmol), MeCN (4 mL) and F_2 (9.6 mmol) with methyl hydrazine (0.0691 g, 1.5 mmol), ethanol (4 mL) after purification recrystallisation from hexane gave *3,5-di-tert-butyl-4-fluoro-1H-pyrazole* (0.148 g, 74 %) as yellow crystals; m.p. 176–178 °C; (Found $[MH]^+$, 199.1605. $C_{11}H_{19}FN_2$ requires: $[MH]^+$, 199.1605); 1H NMR (700 MHz, $CDCl_3$): δ 1.33 (18H, s, CH_3); ^{13}C NMR (176 MHz, $CDCl_3$): δ 28.9 (d, $^4J_{CF}$ 1.8, $C(CH_3)_3$), 31.4 (d, $^3J_{CF}$ 3.4, $C(CH_3)_3$), 142.1 (bm, 3-C) 143.6 (d, $^1J_{CF}$ 243.1, 4-C); ^{19}F NMR (658 MHz, $CDCl_3$): δ -174.5 (s); m/z (EI^+) 198.2 ($[M]^+$, 100 %), 183.2 (66), 127.1 (22), 57.2 (42).

4-Fluoro-5-methyl-3-phenyl-1H-pyrazole (201)



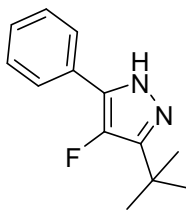
1-Phenylbutane-1,3-dione (0.162g, 1.0 mmol), MeCN (4 mL) and F₂ (9.6 mmol) with methyl hydrazine (0.0691 g, 1.5 mmol), ethanol (4 mL) after purification by column chromatography over silica gel with hexane and ethyl acetate (1:1) as the eluent gave *4-fluoro-5-methyl-3-phenyl-1H-pyrazole* (0.121 g, 69 %) as white crystals; m.p. 136–138 °C; (Found [MH]⁺, 177.0831. C₁₀H₉FN₂ requires: [MH]⁺, 177.0750); ¹H NMR (400 MHz; CDCl₃) 2.04 (3H, s, CH₃), 7.31–7.76 (5H, m, Ar-H), 7.79 (1H, bs, NH); ¹³C NMR (126 MHz; CDCl₃): 8.7 (CH₃), 125.6 (d, ²J_{CF} 3.8, 5-C), 128.1 (Ar), 128.8 (Ar), 129.2 (3-C), 145.1 (1F, d, ¹J_{CF} 246.8, 4-C); ¹⁹F NMR (376 MHz; CDCl₃): δ -179.9 (s); *m/z* (EI⁺) 176.1 ([M]⁺, 100 %), 145.9 (22), 108.1 (17), 77.0 (35).

3-Tert-butyl-4-fluoro-5-methyl-1H-pyrazole (202)



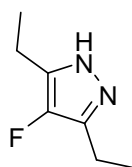
5,5-Dimethylhexane-2,4-dione (0.160 g, 1.0 mmol), MeCN (4 mL) and F₂ (9.6 mmol) with methyl hydrazine (0.0691 g, 1.5 mmol), ethanol (4 mL) after purification by column chromatography over silica gel with hexane and ethyl acetate (1:1) as the eluent gave *3-tert-butyl-4-fluoro-5-methyl-1H-pyrazole* (0.11 g, 71 %) as yellow crystals; m.p. 129–131 °C; (Found: [MH]⁺, 157.1131. C₈H₁₃FN₂ requires: [MH]⁺, 157.1141); ¹H NMR (400 MHz; CDCl₃): δ 1.34 (9H, s, C(CH₃)₃), 2.21 (3H, s, CH₃); ¹³C NMR (126 MHz; CDCl₃): δ 9.11 (CH₃), 29.2 (s, C(CH₃)₃), 31.6 (s, C(CH₃)₃), 131.5 (d, ²J_{CF} 19.4, 5-C), 140.9 (d, ²J_{CF} 15.5, 3-C), 144.4 (d, ¹J_{CF} 241.3, 4-C); ¹⁹F NMR (376 MHz; CDCl₃): δ -179.9 (s); *m/z* (EI⁺) 156.1 ([M]⁺, 100 %), 141.1 (90), 113.1 (21), 101.1 (23).

3-Tert-butyl-4-fluoro-5-methyl-1H-pyrazole (203)



4,4-Dimethyl-1-phenylpentane-1,3-dione (0.204 g, 1.0 mmol), MeCN (4 mL) and F₂ (9.6 mmol) with methyl hydrazine (0.0691 g, 1.5 mmol), ethanol (4 mL) after purification by column chromatography over silica gel with hexane and ethyl acetate (7:3) as the eluent gave *3-tert-butyl-4-fluoro-5-methyl-1H-pyrazole* (0.174 g, 80 %) as a yellow oil; (Found: [MH]⁺, 219.1303. C₁₃H₁₅FN₂ requires: [MH]⁺, 219.1298); ¹H NMR (400 MHz; CDCl₃): δ 1.37 (9H, s, CH₃), 7.44–7.80 (5H, m, Ar-H); ¹³C NMR (126 MHz; CDCl₃): δ 28.9 (C(CH₃)₃), 31.4 (C(CH₃)₃), 125.7 (Ar), 128.0 (Ar), 128.7 (Ar), 134.5 (3-C), 141.1 (5-C), 143.9 (d, ¹J_{CF} 247.3, 4-C); ¹⁹F NMR (376 MHz; CDCl₃): δ -174.7 (s); *m/z* (EI⁺) 218.1 ([M]⁺, 100 %), 203.1 (98), 175.0 (32), 163.1 (36), 87.6 (37).

3,5-Diethyl-4-fluoro-1H-pyrazole (204)



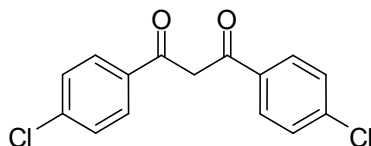
Heptane-3,5-dione (0.128 g, 1.0 mmol), MeCN (4 mL) and F₂ (9.6 mmol) with methyl hydrazine (0.0691 g, 1.5 mmol), ethanol (4 mL) after purification by column chromatography over silica gel with ethyl acetate as the eluent gave *3,5-diethyl-4-fluoro-1H-pyrazole* (0.102 g, 72 %) as pale yellow crystals; m.p. 121–123 °C; (Found: [M]⁺, 142.0893. C₇H₁₁FN₂ requires: [M]⁺, 142.0906); ¹H NMR (400 MHz; CDCl₃): δ 1.21 (6H, t, ³J_{HF} 7.7, CH₂CH₃), 2.58 (4H, q, ³J_{HF} 7.6, CH₂CH₃), 11.5 (1H, bs, NH); ¹³C NMR (126 MHz; CDCl₃): δ 12.7 (CH₂CH₃), 17.5 (CH₂CH₃), 135.0 (bs, 3-C), 144.6 (d, ¹J_{CF} 239.6, 4-C); ¹⁹F NMR (376 MHz; CDCl₃): δ -184.7 (s); *m/z* (EI⁺) 142.6 ([M]⁺, 100 %), 127.0 (90), 113.1 (40), 83.1 (18), 59.1 (22).

7.5 Experimental to Chapter 5

7.5.1 Synthesis of 1,3-Diketones – General Procedure

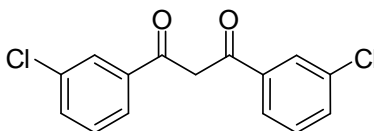
Anhydrous THF (20 mL) and sodium hydride 60 % in mineral oil or lithium bis(trimethylsilyl)amide (2 equiv.) were stirred and cooled (0 °C) for 30 minutes under nitrogen. The benzoate (1.2 equiv.) and acetophenone (1 equiv.) were dissolved in anhydrous THF (2 mL) and added to the anhydrous THF drop-wise. The reaction mixture stirred overnight and quenched with 30 % HCl (15 mL) to give a pale yellow precipitate which was filtered. The solid was then extracted from TBME (3 x 30 mL) and washed with sodium bicarbonate (30 mL) and water (30 mL). The combined extracts were dried over MgSO₄ and the solvent removed by vacuum to give a crude product, which was analysed by ¹⁹F NMR spectroscopy and LC-MS and purified by recrystallisation.

1,3-Bis(4-chlorophenyl)propane-1,3-dione (**210**)¹⁰⁷



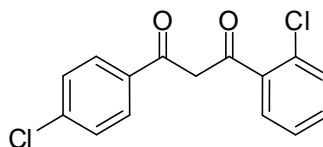
Anhydrous THF (20 mL) and 60 % sodium hydride in mineral oil (1.24 g, 51.7 mmol) with ethyl 4-chlorobenzoate (4.00 g, 25.9 mmol) and 1-(4-chlorophenyl)propane-1,3-dione (5.25 g, 28.5 mmol) after recrystallisation from hexane gave *1,3-bis(4-chlorophenyl)propane-1,3-dione* (6.33 g, 83 %) as yellow crystals; m.p. 196–197 °C [lit. 195–196 °C]; ¹H NMR (400 MHz; CDCl₃): δ 6.76 (2H, s, 2-*H*), 7.45 (4H, d, ³*J*_{CH} 8.0, 3-*H*), 7.90 (4H, d, ³*J*_{CH} 8.1, 2-*H*); ¹³C NMR (176 MHz, (CDCl₃): δ 93.1 (2-*C*), 128.7 (3'-*C*), 129.3 (2'-*C*), 134.0 (1'-*C*), 139.1 (4'-*C*), 184.8 (1-*C*, 3-*C*); *m/z* (ES⁺) 293.1 (100 %, [³⁵Cl, M⁺]), 295.0 (70 %, [³⁷Cl, M⁺]).

1,3-Bis(3-chlorophenyl)propane-1,3-dione (**211**)¹³⁰



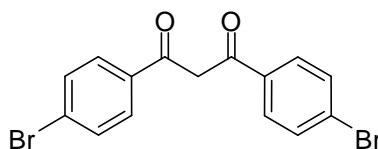
Anhydrous THF (20 mL) and 60 % sodium hydride in mineral oil (0.482 g, 20.1 mmol) with ethyl 2-bromobenzoate (2.53 g, 11.1 mmol) and 1-(3-chlorophenyl)propane-1,3-dione (2.00 g, 10.5 mmol) after recrystallisation from hexane gave *1,3-bis(3-chlorophenyl)propane-1,3-dione* (2.39 g, 66 %) as pale yellow crystals; m.p. 137–139 °C [lit. 135–136 °C]; ¹H NMR (400 MHz; CDCl₃): δ 6.76 (2H, s, 2-H), 7.44 (1H, dd, ³J_{CH} 18.3, 6.0, 5'-H), 7.53 (1H, ddd ³J_{CH} 8.0, ⁴J_{CH} 2.1, 1.1, 4'-H); 7.86 (1H, ddd, ³J_{CH} 7.8, ⁴J_{CH} 1.4, 6'-H), 7.99 (1H, m, 2'-H); ¹³C NMR (126 MHz; CDCl₃): δ 93.7 (2-C), 125.2 (6'-C), 127.6 (2'-C), 130.3 (5'-C), 132.7 (4'-C), 135.3 (3'-C), 137.3 (1'-C), 184.8 (1-C, 3-C); *m/z* (ES⁻) 291.2 (100 %, [³⁵Cl, M⁺]), 293.0 (70 %, [³⁷Cl, M⁺]).

1-(2-Chlorophenyl)-3-(4-chlorophenyl)propane-1,3-dione (212)



Anhydrous THF (20 mL) and 60 % sodium hydride in mineral oil (0.621 g, 25.9 mmol) with ethyl 2-chlorobenzoate (2.43 g, 14.2 mmol) and 1-(4-chlorophenyl)propane-1,3-dione (2.00 g, 12.9 mmol) after recrystallisation from hexane gave *1-(2-chlorophenyl)-3-(4-chlorophenyl)propane-1,3-dione* (2.95 g, 78 %) as white crystals; m.p. 156–157 °C; ¹H NMR (400 MHz; CDCl₃): δ 6.69 (1H, s, 2-H), 7.27–8.01 (8H, m, Ar-H); ¹³C NMR (126 MHz; CDCl₃): δ 73.5 (2-C), 126.4 (Ar), 128.2 (Ar), 129.5 (Ar), 129.8 (Ar), 131.1 (Ar), 134.3 (Ar), 134.6 (Ar), 136.1 (Ar), 138.9 (Ar), 184.8 (1-C, 3-C); *m/z* (ES⁻) 291.1 (100 %, [³⁵Cl, M⁺]), 293.1 (70 %, [³⁷Cl, M⁺]).

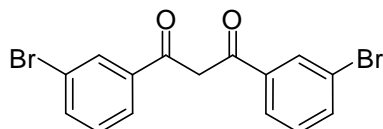
*1,3-Bis(4-bromophenyl)propane-1,3-dione (213)*¹⁰⁷



Anhydrous THF (20 mL) and sodium hydride 60 % in mineral oil (0.571 g, 23.8 mmol) with ethyl 4-bromobenzoate (3.00 g, 13.1 mmol) and 1-(4-bromophenyl)propane-1,3-dione (2.37 g, 11.9 mmol) after recrystallisation from toluene (0.641 g, 74 %) gave *1,3-bis(4-bromophenyl)propane-1,3-dione* as pale yellow crystals; m.p. 186–188 °C [lit.

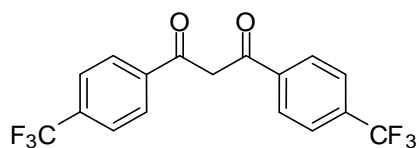
185–186 °C]; ^1H NMR (400 MHz; CDCl_3): δ 6.77 (2H, s, 2-*H*), 7.63 (4H, d, $^3J_{\text{CH}}$ 8.0, 3'-*H*), 7.63 (4H, d, $^3J_{\text{CH}}$ 8.0, 2'-*H*); ^{13}C NMR (126 MHz; CDCl_3): δ 98.1 (2-*C*), 127.8 (4'-*C*), 128.9 (2'-*C*), 132.3 (3'-*C*), 134.4 (1'-*C*), 187.1 (1-*C*, 3-*C*); m/z (ES^+) 382.9 (100 % [^{81}Br , $\text{M} + \text{H}$] $^+$), 384.9 (51 %, [^{79}Br , $\text{M} + \text{H}$] $^+$).

1,3-Bis(3-bromophenyl)propane-1,3-dione (**214**)¹³¹



Anhydrous THF (25 mL) and sodium hydride 60 % in mineral oil (0.482 g, 20.1 mmol) with ethyl 3-bromobenzoate (2.53 g, 11.1 mmol) and 1-(3-bromophenyl)propane-1,3-dione after recrystallisation from toluene gave *1,3-bis(3-bromophenyl)propane-1,3-dione* (2.95 g, 77 %) as pale orange crystals; m.p. 145–147 °C [lit. 148–149 °C]; ^1H NMR (400 MHz; CDCl_3): δ 6.75 (2H, s, 2-*H*), 7.42 (1H, dd $^3J_{\text{CH}}$ 8.0, 5'-*H*), 7.54 (1H, ddd, $^3J_{\text{CH}}$ 7.9, $^4J_{\text{CH}}$ 2.0, 1.0, 6'-*H*); 7.90 (1H, ddd, $^3J_{\text{CH}}$ 8.0, $^4J_{\text{CH}}$ 1.0, 4'-*H*), 8.11 (1H, t, $^3J_{\text{CH}}$ 1.7, 2'-*H*); ^{13}C NMR (126 MHz; CDCl_3): δ 93.7 (2-*C*), 123.2 (3'-*C*), 126.0 (6'-*C*), 130.4 (2'-*C*), 130.5 (5'-*C*), 135.4 (4'-*C*), 137.5 (1'-*C*), 184.6 (1-*C*, 3-*C*); m/z (ES^-) 381.1 (100 % [^{81}Br , $\text{M} + \text{H}$] $^+$), 383.0 (51 %, [^{79}Br , $\text{M} + \text{H}$] $^+$).

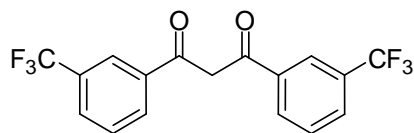
1,3-Bis(4-(trifluoromethyl)phenyl)propane-1,3-dione (**215**)



Anhydrous THF (20 mL) and 60 % sodium hydride in mineral oil (0.705 g, 29.4 mmol) with methyl 4-(trifluoromethyl)benzoate (3.26 g, 16.0 mmol) and 1-(4-(trifluoromethyl)phenyl)ethanone (3.00 g, 15.9 mmol) after recrystallisation from heptane gave *1,3-bis(4-(trifluoromethyl)phenyl)propane-1,3-dione* (4.50 g, 78 %) as a white solid; m.p. 215–217 °C; (Found [MH] $^+$, 360.0587. $\text{C}_{17}\text{H}_{10}\text{F}_6\text{O}_2$ requires: [MH] $^+$, 360.0585); ^1H NMR (400 MHz; CDCl_3): δ 6.85 (2H, s, 2-*H*), 7.77 (4H, d, $^3J_{\text{CH}}$ 8.0, 2'-*H*), 8.03 (4H, d, $^3J_{\text{CH}}$ 8.0, 3'-*H*); ^{13}C NMR (126 MHz; CDCl_3): δ 94.3 (2-*C*), 119.7 (q,

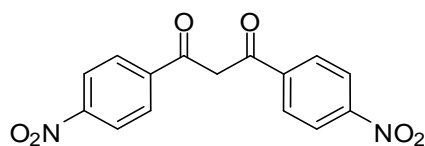
$^1J_{\text{CF}}$ 273.6, $\underline{\text{CF}_3}$), 120.6 (3'-C), 127.9 (2'-C), 133.9 (q, $^2J_{\text{CF}}$ 33.2, 4'-C), 138.6 (1'-C), 184.9 (1-C, 3-C); ^{19}F NMR (376 MHz; CDCl_3): δ -63.5 (s); m/z (ES^-) 359.0.

1,3-Bis(3-(trifluoromethyl)phenyl)propane-1,3-dione (216)



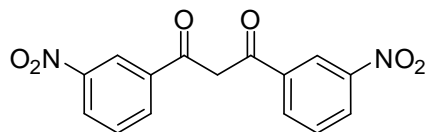
Anhydrous THF (20 mL) and 60 % sodium hydride in mineral oil (0.705 g, 29.4 mmol) with methyl 3-(trifluoromethyl)benzoate (3.26 g, 16.0 mmol) and 1-(3-(trifluoromethyl)phenyl)ethanone (3.00 g, 15.9 mmol) after recrystallisation from heptane gave *1,3-bis(3-(trifluoromethyl)phenyl)propane-1,3-dione* (4.17 g, 72 %) as a white solid solid; m.p. 227–229 °C; (Found $[\text{MH}]^+$, 360.0592. $\text{C}_{17}\text{H}_{10}\text{F}_6\text{O}_2$ requires: $[\text{MH}]^+$, 360.0585); ^1H NMR (400 MHz; CDCl_3): δ 6.87 (1H, s, 2-*H*), 7.58–7.67 (2H, m, 5'-*H*), 7.80–7.87 (2H, m, 4'-*H*), 8.10–8.21 (2H, m, 6'-*H*), 8.23–8.37 (2H, m, 2'-*H*); ^{13}C NMR (126 MHz; CDCl_3): δ 93.7 (2-C), 122.6 (q, $^1J_{\text{CF}}$ 270.6, $\underline{\text{CF}_3}$), 124.4 (q, $^3J_{\text{CF}}$ 5.0, 2'-C), 129.3 (q, $^3J_{\text{CF}}$ 4.0, 4'-C), 129.6 (5'-C), 130.6 (6'-C), 131.2 (q, $^2J_{\text{CF}}$ 33.2, 3'-C), 136.2 (1'-C), 184.8 (1-C, 3-C); ^{19}F NMR (376 MHz; CDCl_3): δ -63.4 (s); m/z (ES^-) 359.3.

1,3-Bis(4-nitrophenyl)propane-1,3-dione (217)



Anhydrous THF (20 mL) and lithium bis(trimethylsilyl)amide (1.0 M in THF) (6.06 mL, 6.06 mmol) with 1-(4-nitrophenyl)ethanone (0.50 g, 3.03 mmol) and 4-nitrobenzoyl chloride (0.562 g, 3.03 mmol) after recrystallisation from hexane/ethyl acetate gave *1,3-bis(4-nitrophenyl)propane-1,3-dione* (0.721 g, 76 %) as orange/brown crystals; m.p. 215–217 °C; (Found $[\text{MH}]^+$, 314.0531. $\text{C}_{15}\text{H}_{10}\text{N}_2\text{O}_6$ requires: $[\text{MH}]^+$, 314.0539); ^1H NMR (400 MHz; CDCl_3): δ 6.92 (2H, s, 2-*H*), 8.17 (4H, d, $^3J_{\text{CH}}$ 8.0, 2'-*H*), 8.35 (4H, d, $^3J_{\text{CH}}$ 8.0, 3'-*H*); ^{13}C NMR (126 MHz; CDCl_3): δ 95.3 (2-C), 124.2 (3'-C), 128.3 (2'-C), 140.6 (1'-C), 159.8 (4'-C), 184.2 (1-C, 1-C); m/z (ES^-) 313.3.

1,3-Bis(3-nitrophenyl)propane-1,3-dione (218)

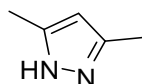


Anhydrous THF (20 mL) and lithium bis(trimethylsilyl)amide (1.0 M in THF) (6.06 mL, 6.06 mmol) with 1-(3-nitrophenyl)ethanone (0.50 g, 3.03 mmol) and 4-nitrobenzoyl chloride (0.562 g, 3.03 mmol) after recrystallisation from toluene gave *1,3-bis(3-nitrophenyl)propane-1,3-dione* (3.99 g, 70 %) as pale orange crystals; m.p. 227–229 °C; (Found $[MH]^+$, 314.0530. $C_{15}H_{10}N_2O_6$ requires: $[MH]^+$, 314.0539); 1H NMR (400 MHz; *d*-DMSO): δ 7.69 (1H, s, 2-*H*), 7.58–7.67 (2H, dd $^3J_{CH}$ 8.0, 5'-*H*), 8.48–8.51 (2H, m, 6'-*H*), 8.65–8.68 (2H, m, 4'-*H*), 8.90 (2H, m, 2'-*H*); ^{13}C NMR (126 MHz; *d*-DMSO): δ 93.7 (2-*C*), 120.0 (2'-*C*), 129.3 (4'-*C*), 129.6 (5'-*C*), 135.6 (6'-*C*), 136.2 (1-*C*), 179.2 (1-*C*, 3-*C*); m/z (ES^-) 313.2.

7.5.2 Synthesis of Pyrazoles – General Procedure

Hydrazine monohydrate or phenyl hydrazine (1.0 equiv.) was added slowly to a mixture of the 1,3-diketone (1.0 equiv.), ethanol (30 mL) and conc. H_2SO_4 (~0.5 mL). The reaction was heated to reflux overnight. On cooling, the solvent was evaporated and water added (50 mL). The organic products were extracted with DCM (3 x 30 mL) and washed with water (30 mL) and NaCl solution (30 mL). The combined extracts were dried over $MgSO_4$ and the solvent removed by vacuum to give a crude product, which was analysed by 1H NMR spectroscopy and GC-MS and purified by recrystallisation.

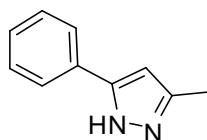
*3,5-Dimethyl-1H-pyrazole (205)*¹³²



Hydrazine monohydrate (1.50 g, 30 mmol), pentane-2,4-dione (3.00 g, 30 mmol) and ethanol (30 mL) after recrystallisation from hexane gave *3,5-dimethyl-1H-pyrazole* (4.21 g, 94 %) as white crystals; m.p. 104–107 °C [lit. 107–109 °C]; 1H NMR (400 MHz; $CDCl_3$): δ 2.31–2.35 (6H, s, CH_3), 5.72 (1H, s, 4-*H*), 11.9 (1H, bs, NH); ^{13}C

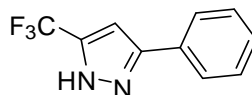
NMR (126 MHz; CDCl₃): δ 13.1 (CH₃), 106.3 (3-C, 5-C), 144.9 (4-C); m/z (EI⁺) 96.1 ([M]⁺, 100 %), 81.1 (16), 54.1 (25), 39.1 (18).

*5-Methyl-3-phenyl-1H-pyrazole (220)*¹³³



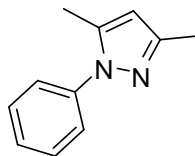
Hydrazine monohydrate (0.62 g, 12.3 mmol), 1-phenylbutane-1,3-dione (2.00 g, 12.3 mmol) and ethanol (30 mL) after recrystallisation from hexane gave *5-methyl-3-phenyl-1H-pyrazole* (1.81 g, 93 %) as white crystals; m.p. 125–127 °C [lit. 126–128 °C]; ¹H NMR (400 MHz; CDCl₃): δ 2.37 (3H, s, CH₃), 6.38 (1H, s, 4-*H*), 7.31–7.34 (1H, m, 4'-*H*), 7.39–7.43 (2H, m, 3'-*H*), 7.71–7.73 (2H, m, 2'-*H*) 11.69 (1H, bs, NH); ¹³C NMR (126 MHz; CDCl₃): δ 14.0 (CH₃), 106.3 (4-C), 127.2 (Ar), 128.3 (Ar), 129.6 (Ar), 136.0 (1'-C), 143.9 (5-C), 150.6 (3-C); m/z (EI⁺) 158.2 ([M]⁺, 100 %), 157.1 (46), 128.1 (38), 77.1 (52).

*3-Phenyl-5-(trifluoromethyl)-1H-pyrazole (221)*¹³⁴



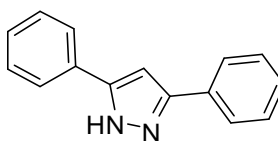
Hydrazine monohydrate (0.69 g, 13.9 mmol), 4,4,4-trifluoro-1-phenylbutane-1,3-dione (3.00 g, 13.9 mmol) and ethanol (30 mL) after recrystallisation from hexane gave *3-phenyl-5-(trifluoromethyl)-1H-pyrazole* (2.74 g, 93 %) as white crystals; m.p. 124–125 °C [lit. 122–123 °C]; ¹H NMR (400 MHz; CDCl₃): δ 6.79 (1H, s, 4'-*H*), 7.42–7.51 (3H, m, 3'-*H*), 7.57–7.60 (2H, m, 2'-*H*), 11.46 (1H, bs, NH); ¹³C NMR (126 MHz; CDCl₃): δ 101.0 (4-C) 123.5 (q, ¹J_{CF} 269.3, CF₃), 127.3 (Ar), 128.1 (Ar), 129.9 (Ar), 133.0 (1'-C), 142.9 (q, ²J_{CF} 34.2, 5-C), 150.5 (3-C); ¹⁹F NMR (376 MHz; CDCl₃): δ -62.2 (s); m/z (EI⁺) 212.1 ([M]⁺, 100 %), 164.0 (43), 143.1 (36), 115.1 (22).

3,5-Dimethyl-1-phenyl-1H-pyrazole (222)



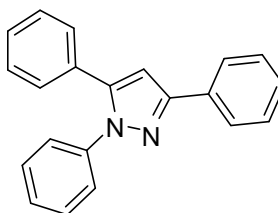
Phenyl hydrazine (1.08 g, 10.0 mmol), pentane-2,4-dione (1.00 g, 10.0 mmol) and ethanol (30 mL) after purification by column chromatography with hexane and ethyl acetate as the eluent (1:1) gave *3,5-dimethyl-1-phenyl-1H-pyrazole* (1.55 g, 90 %) as a red/orange oil; ^1H NMR (400 MHz; CDCl_3): δ 2.27 (3H, s, CH_3), 2.30 (3H, s, CH_3), 6.25 (1H, s, 4-*H*), 7.28–7.43 (4H, m, Ar); ^{13}C NMR (126 MHz; CDCl_3): δ 12.3 (CH_3), 12.5 (CH_3), 106.9 (4-*C*), 124.7 (Ar), 127.2 (Ar), 129.0 (Ar), 139.3 (3-*C*, 5-*C*), 139.9 (1'-*C*), 148.9 (4-*C*); m/z (EI^+) 172 ($[\text{M}]^+$, 100 %), 154 (10), 130 (35), 77 (24), 51 (10).

*3,5-Diphenyl-1H-pyrazole (223)*¹³⁵



Hydrazine monohydrate (0.45 g, 8.9 mmol), 1,3-diphenylpropane-1,3-dione (2.00 g, 8.9 mmol) and ethanol (30 mL) after recrystallisation from toluene gave *3,5-diphenyl-1H-pyrazole* (1.88 g, 96 %) as white crystals; m.p. 198–201 °C [lit. 201 °C]; ^1H NMR (400 MHz; CDCl_3): δ 6.87 (1H, s, 4-*H*), 7.40–7.73 (8H, m, Ar-*H*); ^{13}C NMR (126 MHz; CDCl_3): δ 102.1 (4-*C*), 127.3 (Ar), 128.2 (Ar), 129.6 (Ar), 136.0 (1'-*C*), 148.9 (3-*C*, 5-*C*); m/z (EI^+) 220.0 ($[\text{M}]^+$, 100 %), 190.9 (26), 164.9 (10), 76.9 (24).

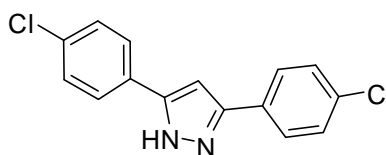
*1,3,5-Triphenyl-1H-pyrazole (224)*¹³⁶



Phenyl hydrazine (1.45 g, 13.4 mmol), 1,3-diphenylpropane-1,3-dione (3.00 g, 13.4 mmol) and ethanol (30 mL) after recrystallisation from ethanol gave *1,3,5-triphenyl-1H-*

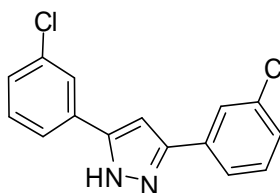
pyrazole (3.14 g, 93 %) as pale orange crystals; m.p. 134–136 °C [lit. 132–139 °C]; ^1H NMR (400 MHz; CDCl_3): δ 6.85 (1H, s, 4-*H*), 7.29–7.96 (15H, m, Ar-H); ^{13}C NMR (126 MHz; CDCl_3): δ 105.2 (4-*C*), 125.3 (Ar), 125.8 (Ar), 128.0 (Ar), 128.3 (Ar), 128.6 (Ar), 128.8 (Ar), 128.9 (Ar), 130.6 (Ar), 133.1 (Ar), 140.2 (Ar), 144.4 (4-*C*), 152.0 (3-*C*, 5-*C*); m/z (EI^+) 296.1 ($[\text{M}]^+$, 100 %), 192.0 (20), 165.0 (22), 88.9 (18), 76.9 (45).

3,5-Bis(4-chlorophenyl)-1*H*-pyrazole (225)¹³⁷



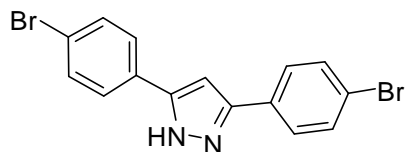
Hydrazine monohydrate (0.262 g, 5.24 mmol), 1,3-bis(4-chlorophenyl)propane-1,3-dione (2.00 g, 5.24 mmol) and ethanol (30 mL) after recrystallisation from toluene gave 3,5-bis(4-chlorophenyl)-1*H*-pyrazole (1.132 g, 87 %) as a white solid; m.p. 242–244 °C [lit. 240–242 °C]; ^1H NMR (400 MHz; CDCl_3): δ 6.89 (1H, s, 4-*H*), 7.45 (4H, d, $^3J_{\text{HH}}$ 8.0, 3'-*H*), 7.88 (4H, d, $^3J_{\text{HH}}$ 8.0, 2'-*H*); ^{13}C NMR (126 MHz; CDCl_3): δ 100.8 (4-*C*), 127.5 (Ar), 129.6 (1'-*C*), 131.8 (4'-*C*), 149.3 (3-*C*, 5-*C*); m/z (ES^+) 289.1.

3,5-Bis(3-chlorophenyl)-1*H*-pyrazole (226)



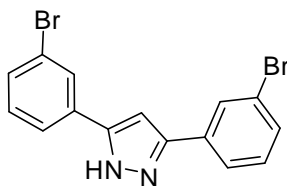
Hydrazine monohydrate (0.128 g, 2.56 mmol), 1,3-bis(3-chlorophenyl)propane-1,3-dione (0.750 g, 2.56 mmol) and ethanol (20 mL) after recrystallisation from hexane gave 3,5-bis(3-chlorophenyl)-1*H*-pyrazole (0.628 g, 85 %) as a white solid; m.p. 204–206 °C; (Found $[\text{M}]^+$ 288.0220 $\text{C}_{15}\text{H}_{10}^{35}\text{Cl}_2\text{N}_2$ requires: $[\text{M}]^+$ 288.0221); ^1H NMR (400 MHz; CDCl_3): δ 6.86 (1H, s, 4-*H*), 7.33–7.40 (4H, m, Ar-H), 7.61–7.65 (2H, m, 6'-*H*), 7.71–7.73 (2H, m, 2'-*H*); ^{13}C NMR (126 MHz; CDCl_3): δ 102.1 (4-*C*), 124.1 (6'-*C*), 125.0 (2'-*C*), 126.5 (4'-*C*), 128.9 (5'-*C*), 131.4 (1'-*C*), 132.2 (3'-*C*), 155.7 (3-*C*, 5-*C*); m/z (ASAP^+) 288.0 (100 %, [^{35}Cl , M^+]), 290.0 (70 %, [^{37}Cl , M^+]).

*3,5-Bis(4-bromophenyl)-1H-pyrazole (227)*⁵⁸



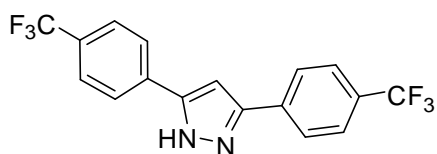
Hydrazine monohydrate (0.131 g, 2.62 mmol, 1,3-bis(4-bromophenyl)propane-1,3-dione (1.00 g, 2.62 mmol) and ethanol (30 mL) after recrystallisation from toluene gave *3,5-bis(4-bromophenyl)-1H-pyrazole* (0.751 g, 76 %) as a white solid; m.p. 257–259 °C [lit. 262 °C]; ¹H NMR (400 MHz; *d*-DMSO) 7.24 (1H, s, 4-*H*), 7.63 (4H, d, ³*J*_{CH} 8.0, 3'-*H*), 7.71 (4H, d, ³*J*_{CH} 8.0, 2'-*H*), 13.45 (1H, s, NH); ¹³C NMR (126 MHz; *d*-DMSO); 105.7 (4-*C*), 132.5 (Ar), 137.0 (4'-*C*), 137.4 (1'-*C*), 148.0 (3-*C*, 5-*C*); *m/z* (ASAP⁺) 380.9 (100 %, [⁸¹Br, M + H]⁺), 375.9 (100 %, [⁷⁹Br, M + H]⁺).

3,5-Bis(3-bromophenyl)-1H-pyrazole (228)



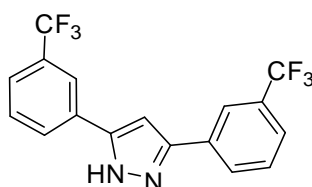
Hydrazine monohydrate (0.065 g, 1.31 mmol), 1,3-bis(3-bromophenyl)propane-1,3-dione (0.50 g, 1.31 mmol) and ethanol (20 mL) after recrystallisation from toluene gave *3,5-bis(3-bromophenyl)-1H-pyrazole* (0.628 g, 85%) as white crystals; m.p. 190–192 °C; (Found [MH]⁺, 375.9213. C₁₅H₁₀⁷⁹Br₂N₂ requires: [MH]⁺, 375.9211); ¹H NMR (400 MHz; CDCl₃): δ 6.72 (1H, s, 4-*H*), 7.31–7.92 (8H, m, Ar-*H*); ¹³C NMR (126 MHz; CDCl₃): δ 101.8 (4-*C*), 123.0 (Ar), 124.7 (Ar), 128.2 (Ar), 130.8 (Ar), 132.0 (Ar), 136.3 (Ar), 143.1 (3-*C*, 5-*C*); *m/z* (ASAP⁺) 380.9 (100 %, [⁸¹Br, M + H]⁺), 375.9 (100 %, [⁷⁹Br, M + H]⁺).

3,5-Bis(4-(trifluoromethyl)phenyl)-1H-pyrazole (229)



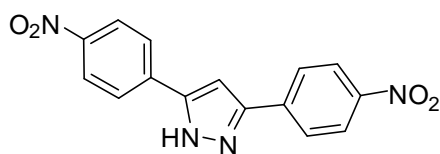
Hydrazine monohydrate (0.417 g, 8.33 mmol), 1,3-bis(4-(trifluoromethyl)phenyl)propane-1,3-dione (3.00 g, 8.33 mmol) and ethanol (30 mL) after recrystallisation from ethanol gave *3,5-bis(4-(trifluoromethyl)phenyl)-1H-pyrazole* (2.60 g, 88 %) as a white solid; m.p. 224–226 °C; (Found $[M]^+$ 356.0742 $C_{17}H_{10}F_6N_2$ requires: $[M]^+$ 356.0748); 1H NMR (400 MHz; *d*-DMSO): δ 7.45 (1H, s, 4-*H*), 7.79 (4H, d, $^3J_{CH}$ 8.0, 3'-*H*), 8.04 (4H, d, $^3J_{CH}$ 8.0, 2'-*H*); ^{13}C NMR (126 MHz; *d*-DMSO): δ 102.3 (4-*C*), 111.6 (q, $^1J_{CF}$ 270.6, \underline{CF}_3), 130.7 (1'-*C*), 131.7 (q, $^3J_{CF}$ 4.1, 3'-*C*), 132.4 (2'-*C*), 140.0 (q, $^2J_{CF}$ 34.2, 4'-*C*), 166.8 (3-*C*, 5-*C*); ^{19}F NMR (376 MHz; $CDCl_3$): δ -61.5 (s); m/z (ES^+) 357.1.

3,5-Bis(3-(trifluoromethyl)phenyl)-1H-pyrazole (**230**)



Hydrazine monohydrate (0.417 g, 8.33 mmol), 1,3-bis(3-(trifluoromethyl)phenyl)propane-1,3-dione (3.00 g, 8.33 mmol) and ethanol (30 mL) after recrystallisation from hexane gave *3,5-bis(3-(trifluoromethyl)phenyl)-1H-pyrazole* (2.60 g, 88 %) as a white solid; m.p. 176–178 °C; (Found $[MH]^+$, 356.0743. $C_{17}H_{10}F_6N_2$ requires: $[MH]^+$, 356.0748); 1H NMR (400 MHz; $CDCl_3$): δ ($CDCl_3$) 6.95 (1H, s, 4-*H*), 7.53–7.99 (8H, m, Ar-*H*); ^{13}C NMR (126 MHz; $CDCl_3$): δ 101.1 (4-*C*), 111.6 (q, $^1J_{CF}$ 305.8, \underline{CF}_3), 122.7 (q, $^3J_{CF}$ 4.0, 3'-*C*), 125.3 (q, $^3J_{CF}$ 4.0, 4'-*C*), 128.9 (6'-*C*), 129.7 (5'-*C*), 151.6 (q, $^2J_{CF}$ 34.2, 3'-*C*), 132.0 (1'-*C*), 154.9 (3-*C*, 5-*C*); ^{19}F NMR (376 MHz; $CDCl_3$): δ -63.3 (s); m/z (ES^+) 357.1.

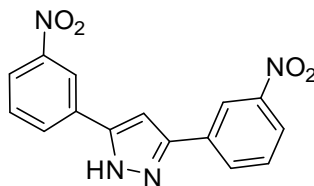
3,5-Bis(4-nitrophenyl)-1H-pyrazole (**231**)¹³⁸



Hydrazine monohydrate (0.0501 g, 1.00 mmol), 1,3-bis(4-nitrophenyl)propane-1,3-dione (0.314 g, 1.00 mmol) and ethanol (20 mL) after recrystallisation from ethanol gave *3,5-bis(4-nitrophenyl)-1H-pyrazole* (0.247 g, 80 %) as a white solid; m.p. 264–

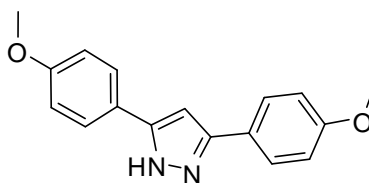
266 °C [lit. 266–268 °C]; ^1H NMR (400 MHz; *d*-DMSO): δ 7.62 (1H, s, 4-*H*), 8.09 (4H, d, $^3J_{\text{CH}}$ 8.0, 2'-*H*), 8.31 (4H, d, $^3J_{\text{CH}}$ 8.0, 3'-*H*); ^{13}C NMR (126 MHz; *d*-DMSO): δ 103.9 (4-*C*), 125.0 (3'-*C*), 126.7 (2'-*C*), 147.3 (1'-*C*), 151.3 (3-*C*, 5-*C*), 152.0 (4'-*C*); m/z (ES^-) 309.2.

3,5-Bis(3-nitrophenyl)-1*H*-pyrazole (232)



Hydrazine monohydrate (0.319 g, 6.36 mmol), 1,3-bis(3-nitrophenyl)propane-1,3-dione (2.00 g, 6.36 mmol) and ethanol (30 mL) after recrystallisation from ethanol gave 3,5-bis(3-nitrophenyl)-1*H*-pyrazole (1.56 g, 79 %) as a white solid; m.p. 255–257 °C; (Found $[\text{MH}]^+$, 310.0704. $\text{C}_{15}\text{H}_{10}\text{N}_2\text{O}_4$ requires: $[\text{MH}]^+$, 310.0702); ^1H NMR (400 MHz; *d*-DMSO): δ 6.81 (1H, s, 4-*H*), 7.71–7.67 (8H, m, Ar-*H*); ^{13}C NMR (126 MHz; *d*-DMSO): δ 99.7 (4-*C*), 121.7 (5'-*C*), 122.2 (4'-*C*), 129.6 (2'-*C*), 132.8 (6'-*C*), 133.4 (1'-*C*), 146.1 (3-*C*, 5-*C*), 147.4 (3-*C*); m/z (ES^-) 309.1.

3,5-Bis(4-methoxyphenyl)-1*H*-pyrazole (233)¹³⁹



Hydrazine monohydrate (0.182 g, 3.52 mmol), 1,3-bis(4-methoxyphenyl)propane-1,3-dione (1.00 g, 3.52 mmol) and ethanol (20 mL) after recrystallisation from ethanol gave 3,5-bis(4-methoxyphenyl)-1*H*-pyrazole (0.945 g, 96 %) as white crystals; m.p. 151–152 °C [lit. 153 °C]; ^1H NMR (400 MHz; CDCl_3): δ 3.82 (6H, s, OCH_3), 6.65 (1H, s, 4-*H*), 6.91 (4H, d, $^3J_{\text{HH}}$ 8.2, 3'-*H*), 7.62 (4H, d, $^3J_{\text{HH}}$ 8.3, 2'-*H*); ^{13}C NMR (176 MHz, CDCl_3): δ 55.1 (OCH_3), 99.7 (4-*C*), 117.3 (3'-*C*), 124.0 (1'-*C*), 127.2 (2'-*C*), 148.5 (3-*C*, 5-*C*), 160.1 (4'-*C*); m/z (ES^+) 281.1.

6.5.3 Ring Fluorination of Pyrazoles using Selectfluor™ – General Procedure

Pyrazole (1 equiv.) and Selectfluor™ (1 equiv.) were dissolved in acetonitrile (5 mL) and the mixture heated by microwave irradiation for 15 minutes at 90 °C. The mixture was then extracted with DCM (3 x 50 mL) and washed with sodium bicarbonate (30 mL) and water (30 mL). The combined extracts were dried (MgSO₄) and evaporated to give a crude product which was analysed by ¹⁹F NMR spectroscopy and GC-MS and purified by column chromatography on silica gel or alumina.

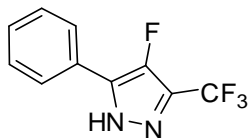
7.5.4 Ring Fluorination of Pyrazoles Using Fluorine – General Procedure

The substrate (1 equiv.) was dissolved in acetic acid or acetonitrile (30 mL) in a Teflon reaction vessel fitted with a F₂ delivery tube, stirrer bar and exhaust tube connected to a scrubber containing soda lime. The system was purged with N₂ gas for 10 minutes before F₂ (10 % in N₂) (2 or 4 equiv.) was allowed to flow using at a prescribed flow rate (30 mL/ min) using a Brooks Instruments™ mass flow controller for 4 h. On completion of the reaction, N₂ was purged through the system for a further 10 minutes. The mixture was then extracted from DCM (3 x 30 mL) and washed with sodium bicarbonate (30 mL) and water (30 mL). The combined extracts were then dried (MgSO₄) and the solvent evaporated under vacuum. The crude material was then purified by column chromatography on silica gel with DCM or ethyl acetate and hexane as the eluent. The data was compared to pure samples and literature data. The product was then washed by water (30 mL) and extracted by DCM (30 mL). The organic extracts were then washed with saturated NaHCO₃ (50 mL) and dried over MgSO₄ and the solvent removed by vacuum to give a crude product, which was analysed by ¹⁹F NMR spectroscopy and GC-MS.

4-Fluoro-5-methyl-3-phenyl-1H-pyrazole (201)

5-Methyl-3-phenyl-1H-pyrazole (0.30 g, 1.90 mmol), Selectfluor™ (0.80 g, 2.28 mmol) and MeCN (5 mL), after column chromatography on alumina using 3:7 ethyl acetate and hexane (3 : 7) as eluent, gave *4-fluoro-5-methyl-3-phenyl-1H-pyrazole* (0.11 g, 33 %) as white crystals; spectral and physical data as above.

4-Fluoro-5-phenyl-3-(trifluoromethyl)-1H-pyrazole (235)



5-Phenyl-3-(trifluoromethyl)-1H-pyrazole (0.30 g, 1.41 mmol), Selectfluor™ (0.60 g, 1.69 mmol) and MeCN (5 mL) after purification by column chromatography on alumina using ethyl acetate and hexane (3:7) as eluent gave *4-fluoro-5-phenyl-3-(trifluoromethyl)-1H-pyrazole* (0.15 g, 46 %) as white crystals; m.p. 144–146 °C; (Found $[MH]^+$, 231.0547. $C_{10}H_6F_4N_2$ requires: $[MH]^+$, 231.0545); 1H NMR (400 MHz; $CDCl_3$): δ 7.43–7.46 (1H, m, 4'-H), 7.49–7.51 (2H, m, 3'-H), 7.60–7.61 (2H, m, 2'-H), 10.5 (1H, bs, NH); ^{13}C NMR (126 MHz; $CDCl_3$): δ 120.5 (qd, $^1J_{CF}$ 286.5, $^3J_{CF}$ 3.4, \underline{CF}_3), 125.6 (2'-C), 125.7 (qm, $^1J_{CF}$ 4.5, 3-C), 129.5 (1'-C), 129.7 (3'-C), 129.9 (4'-C), 130.5 (dm, $^2J_{CF}$ 19.0, 5-C), 142.9 (dq, $^1J_{CF}$ 256.7, $^3J_{CF}$ 2.7, 4-C); ^{19}F NMR (376 MHz; $CDCl_3$): δ -174.9 (1F, s, CF), -62.6 (3F, s, \underline{CF}_3) (s); m/z (EI^+) 230.1 (M^+ , 100), 212.0 (100), 164.0 (45), 143.0 (32), 77.1 (34).

4-Fluoro-3,5-dimethyl-1-phenyl-1H-pyrazole (195)

Reaction of 3,5-dimethyl-1-phenyl-1H-pyrazole (0.30 g, 1.74 mmol) and Selectfluor (0.617 g, 1.74 mmol) in MeCN to give an orange/brown oil which was purified by column chromatography over silica gel with 1:1 hexane and ethyl acetate as the eluent to give *4-fluoro-3,5-dimethyl-1-phenyl-1H-pyrazole* (0.133 g, 40 %) as a yellow oil; spectral and physical data as above.

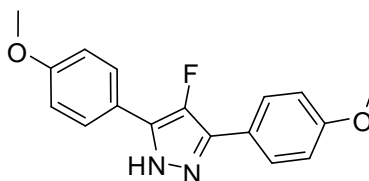
4-Fluoro-3,5-diphenyl-1H-pyrazole (196)

3,5-Diphenyl-1H-pyrazole (0.30 g, 1.36 mmol), Selectfluor (0.482 g, 1.36 mmol) and MeCN, after column chromatography on silica gel using hexane and ethyl acetate (1 : 1) as the eluent, gave *4-fluoro-3,5-diphenyl-1H-pyrazole* (0.135 g, 42 %) as pale yellow crystals; spectral and physical data as above.

4-Fluoro-1,3,5-triphenyl-1H-pyrazole (197)

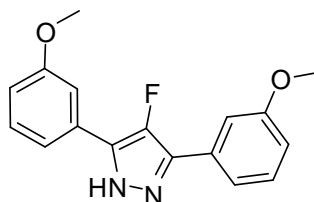
Reaction of 1,3,5-triphenyl-1H-pyrazole (0.30 g, 1.01 mmol) and Selectfluor (0.80 g, 2.28 mmol) in MeCN to give a red/brown solid which was purified by column chromatography with DCM as the eluent to give *4-fluoro-1,3,5-triphenyl-1H-pyrazole* (0.149 g, 47 %) as orange crystals; spectral and physical data as above.

4-Fluoro-3,5-bis(4-methoxyphenyl)-1H-pyrazole (246)



3,5-Bis(4-methoxyphenyl)-1H-pyrazole (0.20 g, 0.713 mmol), Selectfluor™ (0.253 g, 0.713 mmol) and acetonitrile (5 mL) after purification by column chromatography using ethyl acetate and heptane (3:2) as the eluent gave *4-fluoro-3,5-bis(4-methoxyphenyl)-1H-pyrazole* (0.096 g, 45 %) as white crystals; m.p. 151–153 °C; (Found $[M]^+$, 299.1217. $C_{17}H_{15}FN_2O_2$ requires: $[M]^+$, 299.1196); 1H NMR (400 MHz; $CDCl_3$): δ 3.82 (6H, s, OCH_3), 7.00 (4H, d $^3J_{HH}$ 7.9, 3'-H), 7.62 (4H, d, $^3J_{HH}$ 8.2, 2'-H); ^{13}C NMR (176 MHz, $CDCl_3$): δ 55.5 (OCH_3), 114.5 (3'-C), 122.0 (d, $^2J_{CF}$ 22.0, 3-C, 5-C), 127.2 (2'-C), 127.2 (1'-C), 140.0 (d, $^1J_{CF}$ 248.0, 4-C), 159.7 (4'-C); ^{19}F NMR (658 MHz, $CDCl_3$): δ -177.1 (s); m/z (ES^+) 299.2.

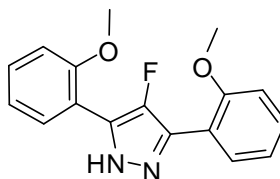
4-Fluoro-3,5-bis(3-methoxyphenyl)-1H-pyrazole (247)



3,5-Bis(3-methoxyphenyl)-1H-pyrazole (0.20 g, 0.713 mmol), Selectfluor™ (0.253 g, 0.713 mmol) and acetonitrile (5 mL) after purification by column chromatography with hexane/ethyl acetate (7:3) as the eluent and subsequent recrystallisation from hexane gave *4-fluoro-3,5-bis(3-methoxyphenyl)-1H-pyrazole* (0.066 g, 31 %) as white crystals; m.p. 145–147 °C; (Found $[MH]^+$, 299.1971. $C_{17}H_{15}FN_2O_2$ requires: $[MH]^+$, 299.1996);

^1H NMR (400 MHz; CDCl_3): δ 6.96–6.98 (2H, m, 4'-H), 7.36–7.41 (6H, m, Ar-H), 13.4 (1H, bs, NH); ^{13}C NMR (176 MHz, (CDCl_3): δ 55.1 (OCH_3), 110.4 (2'-C), 114.0 (4'-C), 121.1 (6-C), 126.3 (5'-C), 129.4 (1'-C), 136.7 (d, $^2J_{\text{CF}}$ 19.5, 3-C, 5-C), 140.3 (d, $^1J_{\text{CF}}$ 251.1, 4-C), 160.3 (3'-C); ^{19}F NMR (658 MHz, CDCl_3): δ -174.7 (s); m/z (ES^-) 297.4.

4-Fluoro-3,5-bis(2-methoxyphenyl)-1H-pyrazole (248)

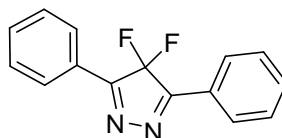


3,5-Bis(4-methoxyphenyl)-1H-pyrazole (0.20 g, 0.713 mmol), SelectfluorTM (0.253 g, 0.713 mmol) and acetonitrile (5 mL) after purification by column chromatography using ethyl acetate and heptane (3:2) as the eluent gave *4-fluoro-3,5-bis(2-methoxyphenyl)-1H-pyrazole* (0.089 g, 42 %) as white crystals; m.p. 128–131 °C; (Found $[\text{MH}]^+$, 299.1248. $\text{C}_{17}\text{H}_{15}\text{FN}_2\text{O}_2$ requires: $[\text{MH}]^+$, 299.1996); ^1H NMR (400 MHz; CDCl_3): δ 3.94 (6H, s, OCH_3), 7.03–7.05 (4H, m, Ar-H), 7.06–7.10 (2H, m, 4'-H), 7.33–7.38 (2H, m, 6'-H), 11.1 (1H, s, NH); ^{13}C NMR (176 MHz, (CDCl_3): δ 56.1 (OCH_3), 111.6 (Ar), 121.4 (d, $^2J_{\text{CF}}$ 18.1, 3-C, 5-C), 121.4 (4'-C), 129.6 (6'-C), 140.0 (d, $^1J_{\text{CF}}$ 251.5, 4-C), 156.0 (1'-C); ^{19}F NMR (658 MHz, CDCl_3): δ -169.0 (s); m/z (ES^+) 299.2.

7.5.5 Di-fluorination of pyrazoles using SelectfluorTM – General Procedure

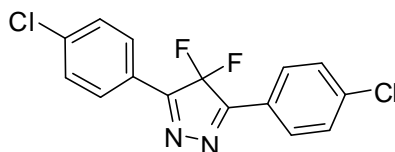
Pyrazole (1 equiv.) and SelectfluorTM (2 equiv.) were dissolved in acetonitrile (5 mL) and the mixture heated by microwave irradiation for 15 minutes at 90 °C. The mixture was then extracted from DCM (3 x 50 mL) and washed with sodium bicarbonate (30 mL) and water (30 mL). The combined extracts were dried (MgSO_4) and evaporated to give a crude product which was analysed by ^{19}F NMR spectroscopy and GC-MS and purified by column chromatography on silica gel.

4,4-Difluoro-3,5-diphenyl-4H-pyrazole (249)



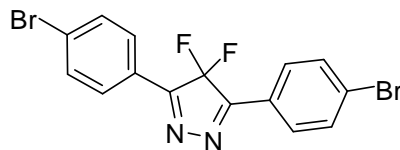
3,5-Diphenyl-1H-pyrazole (0.50 g, 2.27 mmol), Selectfluor™ (1.61 g, 4.54 mmol) and acetonitrile (5 mL) after purification by column chromatography with DCM as to eluent gave *4,4-difluoro-3,5-diphenyl-4H-pyrazole* (0.302 g, 52 %) as yellow crystals; m.p. 105–107 °C; (Found $[MH]^+$, 257.0894. $C_{15}H_{10}F_2N_2$ requires: $[MH]^+$, 257.0890); 1H NMR (400 MHz; $CDCl_3$): δ 7.67–7.44 (6H, m, Ar-H), 8.15–8.06 (4H, m, Ar-H), ^{13}C NMR (126 MHz; $CDCl_3$): δ 125.6 (t, $^1J_{CF}$ 267.5, 1-C), 128.3 (4-C), 129.5 (5-C), 133.1 (6-C), 162.1 (t, $^2J_{CF}$ 23.1, 2-C), ^{19}F NMR (376 MHz; $CDCl_3$): δ -116.3 (s); m/z (EI^+) 256.1 ($[M]^+$, 100 %), 153.0 (45), 103.1 (99), 77.1 (36).

4,4-Difluoro-3,5-bis(4-chlorophenyl)-4H-pyrazole (250)



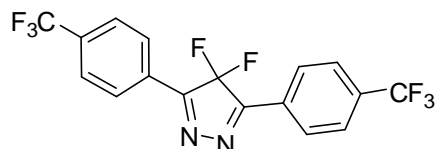
3,5-Bis(4-chlorophenyl)-1H-pyrazole (0.20 g, 0.694 mmol), Selectfluor™ (0.49 g, 1.38 mmol) and acetonitrile (5 mL) after purification by column chromatography with hexane and ethyl acetate (7:3) as the eluent gave *4,4-difluoro-3,5-bis(4-chlorophenyl)-4H-pyrazole* (0.123 g, 54 %) as yellow crystals; m.p 202–204 °C; Found $[MH]^+$, 324.0038. $C_{15}H_8N_2F_2^{35}Cl_2$ requires: $[MH]^+$, 324.0033); 1H NMR (700 MHz; $CDCl_3$): δ 7.55 (4H, d, $^3J_{HH}$ 8.6, 3'-H), 8.06 (4H, d, $^3J_{HH}$ 8.8, 2'-H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 124.1 (4'-C), 127.0 (t, $^1J_{CF}$ 267.4, 4-C), 129.9 (2'-C), 130.0 (3'-C), 140.0 (1'-C), 161.9 (t, $^2J_{CF}$ 23.0, 3-C, 5-C); ^{19}F NMR (376 MHz; $CDCl_3$): δ -116.7 (s); m/z (AP^+) 324.0 (100 %, $[^{35}Cl, M^+]$, 326.0 (70 %, $[^{37}Cl, M^+]$).

4,4-Difluoro-3,5-bis(4-bromophenyl)-4H-pyrazole (251)



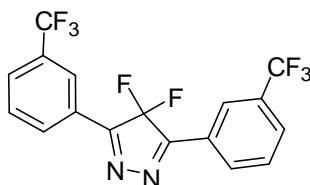
3,5-Bis(4-bromophenyl)-1H-pyrazole (0.20 g, 0.529 mmol), Selectfluor™ (0.375 g, 1.06 mmol) and acetonitrile (5 mL) after purification by column chromatography with heptane and ethyl acetate (1:1) as the eluent gave *4,4-difluoro-3,5-bis(4-bromophenyl)-4H-pyrazole* (0.114 g, 54 %) as yellow crystals; m.p 172–174 °C; (Found $[MH]^+$, 412.. $C_{15}H_8^{79}Br_2F_2N_2$ requires: $[MH]^+$, 412.9101); 1H NMR (400 MHz; $CDCl_3$): δ 7.68 (4H, d, $^3J_{HH}$ 8.1, 3'-H), 7.96 (4H, d, $^3J_{HH}$ 8.2, 2'-H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 124.0 (4'-C), 125.9 (t, $^1J_{CF}$ 252.5, 4-C), 128.4 (1'-C), 129.8 (2'-C), 133.6 (3'-C), 162.1 (t, $^2J_{CF}$ 23.2, 3-C, 5-C); ^{19}F NMR (376 MHz; $CDCl_3$): δ -117.3 (s); m/z (ES^+) 415.0 (100 %, $[^{81}Br, M + H]^+$), 413.0 (52 %, $[^{79}Br, M + H]^+$).

4,4-Difluoro-3,5-bis(4-(trifluoromethyl)phenyl)-4H-pyrazole (252)



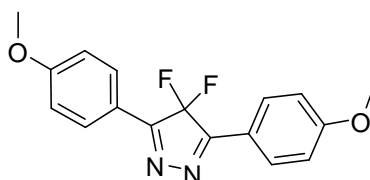
3,5-Bis(4-(trifluoromethyl)phenyl)-1H-pyrazole (0.20 g, 0.561 mmol), Selectfluor™ (0.398 g, 1.12 mmol) and acetonitrile (5 mL) after purification by column chromatography with hexane and ethyl acetate (7:3) as the eluent gave *4,4-difluoro-3,5-bis(4-(trifluoromethyl)phenyl)-4H-pyrazole* (0.112 g, 51 %) as pale yellow crystals; m.p 178–180 °C; (Found $[MH]^+$, 393.0559. $C_{17}H_9N_2F_5$ requires: $[MH]^+$, 393.0560); 1H NMR (400 MHz; $CDCl_3$): δ 7.85 (4H, d, $^3J_{HH}$ 8.2, 3'-H), 8.26 (4H, d, $^3J_{HH}$ 8.1, 2'-H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 121.5 (q, $^1J_{CF}$ 272.7, \underline{CF}_3), 124.8 (t, $^1J_{CF}$ 267.8, 4-C), 128.9 (Ar), 134.9 (q, $^2J_{CF}$ 33.0, 4'-C), 162.1 (t, $^2J_{CF}$ 23.2, 3-C, 5-C); ^{19}F NMR (376 MHz; $CDCl_3$): δ -63.8 (3F, s, CF_3), -118.3 (1F, s, CF); m/z (AP^+) 393.0.

4,4-Difluoro-3,5-bis(3-(trifluoromethyl)phenyl)-4H-pyrazole (253)



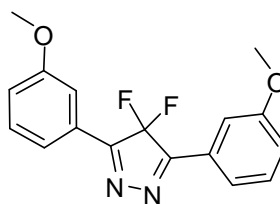
3,5-Bis(3-(trifluoromethyl)phenyl)-1H-pyrazole (0.20 g, 0.564 mmol), Selectfluor™ (0.389 g, 1.13 mmol) and acetonitrile (5 mL) after purification by column chromatography with hexane and ethyl acetate (7:3) as the eluent gave *4,4-difluoro-3,5-bis(3-(trifluoromethyl)phenyl)-4H-pyrazole* (0.097 g, 44 %) as yellow crystals; m.p 122–124 °C; (Found $[MH]^+$, 393.0639. $C_{17}H_9N_2F_2$ requires: $[MH]^+$, 393.0638); 1H NMR (400 MHz; $CDCl_3$): δ 7.73 (2H, m, Ar-H), 7.88 (2H, m, Ar-H), 8.22 (2H, m, Ar-H), 7.39 (2H, s, Ar-H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 121.0 (q, $^1J_{CF}$ 270.9, \underline{CF}_3), 125.1 (q, $^3J_{CF}$ 3.8, Ar), 127.7 (t, $^1J_{CF}$ 267.7, 4-C), 129.0 (q, $^3J_{CF}$ 3.6, Ar), 130.0 (Ar), 131.3 (Ar), 131.9 (q, $^2J_{CF}$ 32.8, 3'-C), 161.8 (t, $^2J_{CF}$ 23.2, 3-C, 5-C); ^{19}F NMR (376 MHz; $CDCl_3$): δ -63.5 (3F, s, CF_3), -117.3 (1F, s, CF); m/z (EI^+) 392.0 ($[M]^+$, 100 %), 347.0 (28), 278.0 (25), 176.0 (88).

4,4-Difluoro-3,5-bis(4-methoxyphenyl)-4H-pyrazole (254)



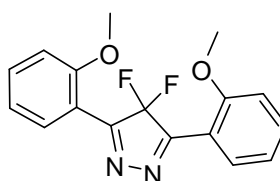
3,5-Bis(4-methoxyphenyl)-1H-pyrazole (0.20 g, 0.713 mmol), Selectfluor™ (0.505 g, 1.43 mmol) and acetonitrile (5 mL) after purification by column chromatography with heptane and ethyl acetate (1:1) as the eluent gave *4,4-difluoro-3,5-bis(4-methoxyphenyl)-4H-pyrazole* (0.101 g, 45 %) as yellow crystals; m.p 178–180 °C; (Found $[MH]^+$, 317.1106. $C_{17}H_{14}F_2N_2O_2$ requires: $[MH]^+$, 317.1102); 1H NMR (400 MHz; $CDCl_3$): δ 3.90 (6H, s, OCH_3), 7.03 (4H, d, $^3J_{HH}$ 8.0, 3'-C), 8.05 (4H, d, $^3J_{HH}$ 9.0, 2'-C); ^{13}C NMR (176 MHz, ($CDCl_3$): δ 55.7 (OCH_3), 118.8 (1'-C), 126.3 (t, $^1J_{CF}$ 266.6, 4-C), 130.3 (2'-C), 161.4 (t, $^2J_{CF}$ 23.1, 3-C, 5-C), 163.6 (4'-C); ^{19}F NMR (658 MHz, $CDCl_3$): δ -114.9 (s); m/z (ES^+) 317.1.

4,4-Difluoro-3,5-bis(3-methoxyphenyl)-4H-pyrazole (255)



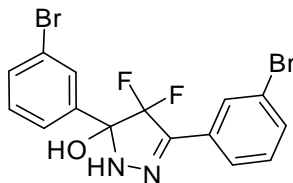
3,5-Bis(3-methoxyphenyl)-1H-pyrazole (0.20 g, 0.713 mmol), Selectfluor™ (0.505 g, 1.43 mmol) and acetonitrile (5 mL) after purification by column chromatography with hexane and ethyl acetate (7:3) as the eluent gave *4,4-difluoro-3,5-bis(3-methoxyphenyl)-4H-pyrazole* (0.097 g, 43 %) as a yellow oil; (Found $[MH]^+$ 317.1098 $C_{17}H_{14}F_2N_2O_2$ requires: $[MH]^+$ 317.1102); 1H NMR (400 MHz; $CDCl_3$): δ 3.90 (6H, s, OMe), 7.16 (2H, ddd, $^2J_{HH}$ 8.4, $^3J_{CH}$ 2.6, 4'-H), 7.46 (2H, td, $^2J_{HH}$ 7.9, $^3J_{HH}$ 0.5, 5'-H), 7.66 (4H, m, 6'-H); ^{13}C NMR (176 MHz, ($CDCl_3$): δ 55.7 (OCH₃), 112.3 (Ar), 120.2 (Ar), 121.3 (Ar), 126.98 (t, $^1J_{CF}$ 285.4, 4-C), 130.5 (1'-C), 160.3 (t, $^2J_{CF}$ 25.9, 3-C, 5-C); ^{19}F NMR (658 MHz, $CDCl_3$): δ -116.3 (s); m/z (ES^+) 317.

4,4-Difluoro-3,5-bis(2-methoxyphenyl)-4H-pyrazole (256)



3,5-Bis(2-methoxyphenyl)-1H-pyrazole (0.20 g, 0.713 mmol), Selectfluor™ (0.505 g, 1.43 mmol) and acetonitrile (5 mL) after purification by column chromatography with ethyl acetate and heptane (3:2) as the eluent gave *4,4-difluoro-3,5-bis(2-methoxyphenyl)-4H-pyrazole* (0.110 g, 49 %) as a yellow oil; (Found $[MH]^+$, 317.1094. $C_{17}H_{14}F_2N_2O_2$ requires: $[MH]^+$, 317.1101); 1H NMR (400 MHz; $CDCl_3$): δ 3.97 (6H, s, OCH₃), 7.05–7.10 (4H, m, Ar-H), 7.45–7.51 (2H, m, 5'-H), 8.00–8.07 (2H, m, 4'-H); ^{13}C NMR (176 MHz, ($CDCl_3$): δ 56.2 (OCH₃), 112.5 (3'-C), 121.0 (5'-C), 124.1 (t, $^1J_{CF}$ 270.6, 4-C), 131.1 (6'-C), 134.0 (4'-C), 160.1 (2'-C) 161.3 (t, $^2J_{CF}$ 24.1, 3-C, 5-C); ^{19}F NMR (658 MHz, $CDCl_3$): δ -119.1 (s); m/z (ES^+) 317.3.

3,5-bis(3-bromophenyl)-4,4-difluoro-4,5-dihydro-1H-pyrazol-5-ol (258)



3,5-Bis(3-bromophenyl)-1H-pyrazole (0.20 g, 0.529 mmol), Selectfluor™ (0.375 g, 1.06 mmol) and acetonitrile (5 mL) after purification by column chromatography with DCM as the eluent gave *3,5-bis(3-bromophenyl)-4,4-difluoro-4,5-dihydro-1H-pyrazol-5-ol* (0.051 g, 24 %) as a yellow oil; (Found $[MH]^+$, 430.9215. $C_{15}H_{10}^{79}Br_2F_2N_2O$ requires: $[MH]^+$, 430.9206); 1H NMR (400 MHz; $CDCl_3$): δ 6.61 (1H, bs, OH), 7.26–7.34 (2H, m, Ar), 7.51–7.55 (1H, m, Ar), 7.56–7.61 (2H, m, Ar), 7.69–7.72 (1H, m, Ar), 7.81–7.83 (1H, m, Ar), 7.97–7.99 (1H, m, Ar); ^{13}C NMR (126 MHz; $CDCl_3$): δ 127.9 (d, $^1J_{CF}$ 246.3, 2-C), 123.2 (Ar), 124.2 (Ar), 126.8 (Ar), 128.0 (Ar), 130.5 (Ar), 130.8 (Ar), 131.0 (Ar), 161.5 (t, $^2J_{CF}$ 23.4, 1-C), 185.8 (t, $^2J_{CF}$ 27.4, 3-C); ^{19}F NMR (376 MHz; $CDCl_3$): δ -101.9– -126.9 (AB, J_{AB} 127.7); m/z (ES^+) 432.8 (100 %, $[^{81}Br, M + H]^+$), 430.0 (51 %, $[^{79}Br, M + H]^+$).

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